AN ABSTRACT OF THE DISSERTATION OF

Nadine Chauyi Lee for the degree of Doctor of Philosophy in Chemistry presented on January 6 1998.

Title: Synthetic Studies on Necic Acids of Pyrrolizidine Alkaloids

Redacted for Privacy

Abstract approved: _____

James D. White

An asymmetric synthesis of (+)-nemorensic acid (**25**) is described in which intramolecular conjugate addition of an alkoxide to the α,β-unsaturated ester **150** was the key step. The anion **150** was generated from desilylation of **142**, which was synthesized from the monoterpene (*R*)-(+)-citronellal (**102**). The synthesis proved that the original stereochemical assignments made to nemorensine as **17** or **23** and to retroisosenine as **18** are incorrect, and that the necic acid constituent of the pyrrolizidine alkaloid (+)-nemorensine possesses the stereochemistry shown in (+)-**25**. An X-ray crystallographic analysis of nemorensine together with this synthetic work has established unambiguously that the complete stereostructure of the natural alkaloid is correctly represented by **1**.

An asymmetric synthesis of 2-*epi*-swazinecic acid (**181**) and an approach towards the asymmetric synthesis of swazinecic acid (**50**) are presented starting from the monoterpene (*S*)-(-)-citronellal (**157**). Although the configuration of the

tertiary alcohol in 2-*epi*-swazinecic acid (**181**) is the reverse of that in swazinecic acid (**50**), it is shown that the configuration of this stereocenter can be inverted by changing the sequence of two Grignard additions. In the revised route towards swazinecic acid (**50**), failure to effect selective hydrolysis of the more exposed ester function of **192** required that differentiation of the ester termini be accomplished by ozonolysis of **190** in the presence of benzyl alcohol instead of methyl alcohol. The resultant benzyl ester **202** was selectively cleaved by hydrogenolysis to produced the desired monocarboxylic acid **203**. The latter was lactonized under Mukaiyama's conditions to afford **204** which was subsequently converted to swazinecic acid (**50**).

Synthetic Studies on Necic Acids of Pyrrolizidine Alkaloids

by

Nadine Chauyi Lee

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degree of

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APPROVED:

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Major Professor, representing Chemistry

Redacted for Privacy

Chair of the Department of Chemistry

Redacted for Privacy

Dean of Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes the release of my dissertation to any reader upon request.

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Nadine Chauyi Lee, Author

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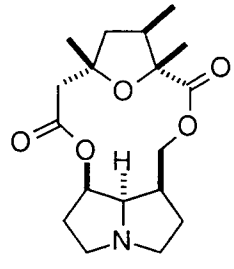
For my parents

SYNTHETIC STUDIES ON NECIC ACIDS OF PYRROLIZIDINE ALKALOIDS

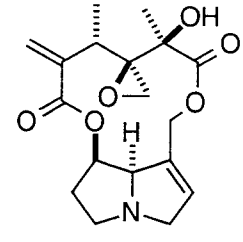
CHAPTER I

GENERAL INTRODUCTION

(+)-Nemorensine (**1**)[1] and (-)-swazine (**2**)[2] belong to the broadly distributed family of pyrrolizidine alkaloids that have been shown to possess powerful hepatotoxic and carcinogenic properties.[3-8] These alkaloids are widespread in nature and it is estimated that the potential number of alkaloid-containing species are as high as 6000, or 3% of the world's flowering plants.[9] To date, there are at least 100-150 pyrrolizidine alkaloids that have been identified in over 150 plant species and nearly 70 genera.[3,6,9] The hepatotoxicity of these alkaloids has caused large-scale death in grazing cattle and presents a potentially serious human health problem.[3-8] Due to the toxicity of pyrrolizidine alkaloids and their consequent environmental health hazard, much attention has been drawn to this area.



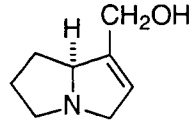
(+)-Nemorensine (**1**)



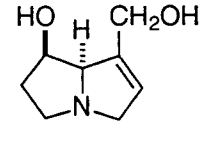
(-)-Swazine (**2**)

Human poisoning by pyrrolizidine alkaloids has been documented in Europe, Africa, Central Asia, and the U.S.[3,4] One of most severe outbreaks of pyrrolizidine alkaloid poisoning occurred in Afghanistan in 1974. Around 35,000 people in 98 villages in a remote area of northwest Afghanistan were affected by consumption of bread made from wheat contaminated with pyrrolizidine alkaloids.[10,11] There are two main sources of human exposure to toxic pyrrolizidine alkaloids.[3,4] The most important of these is consumption of cereal grains, such as wheat and millet, contaminated with the seed or other parts of plants containing these alkaloids. A second source is the consumption for medicinal or dietary purposes of herbs containing the alkaloids, either as the plant itself or as an infusion. It has also been found that pyrrolizidine alkaloids can enter the food chain through milk[12] from cattle that graze on tansy and through honey[13] acquired by bees from pyrrolizidine containing plants.

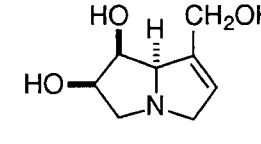
Many pyrrolizidine alkaloids are lactones or esters derived from amino alcohols such as supinidine (**3**), retronecine (**4**) and crotanecine (**5**) by esterification with a variety of branched chain, usually hydroxylated aliphatic acids. The alkaloids themselves may be monoesters, diesters, or cyclic dilactones. A large number of pyrrolizidine alkaloids have been isolated as macrocyclic dilactones, in which a pyrrolizidine diol (necine base) is esterified with a dicarboxylic acid (necic acid) to produce an eleven-to-fourteen membered ring.[3] Examples include merenskine *N*-oxide (**6**),[14] madurensine (**7**),[15,16] and jacobine (**8**).[17,18]



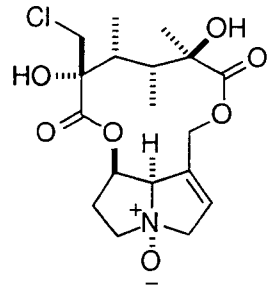
Supinidine (**3**)



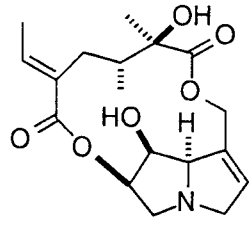
Retronecine (**4**)



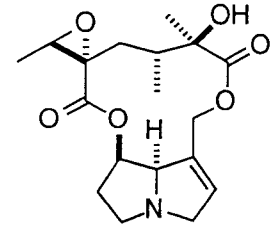
Crotanecine (**5**)



Merenskine *N*-oxide (**6**)

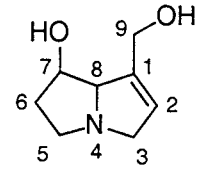


Madurensine (**7**)



Jacobine (**8**)

A structural feature that is required for toxicity in pyrrolizidine alkaloids is unsaturation in the 1,2-position as shown in **9**, and at least one of the hydroxyl groups must be esterified. The endocyclic C-1,2 olefin functionality is essential for the toxic effects of the alkaloids.[19-22]



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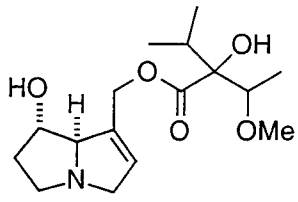
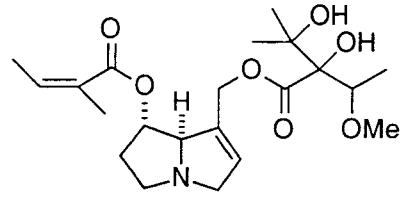
The toxicity of pyrrolizidine alkaloids can be classified according to their structures. In general, monoesters, such as heliotrine (**10**),[23,24] are least toxic. Non-cyclic diesters, such as lasiocarpine (**11**),[23,24] are of intermediate toxicity. The most toxic alkaloids are usually the cyclic dilactones such as retrorsine (**12**)[25] and monocrotaline (**13**).[26] In alkaloids such as senkirkine (**14**),[27] the ketonic character of the eight-membered ring is diminished through interaction of the carbonyl group with the lone pair of electrons on the nitrogen atom. This alkaloid is about one-seventh as toxic as retrorsine (**12**).[28] Alkaloids that have

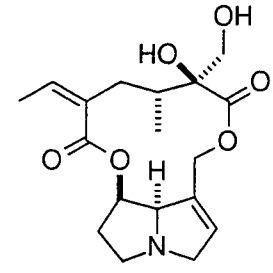
no double bond in the pyrrolizidine subunit, such as platyphylline (**15**),[29] are not toxic.[22]



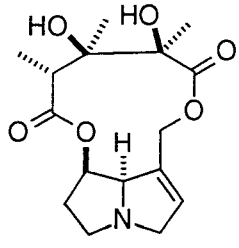
Heliotrine (**10**)



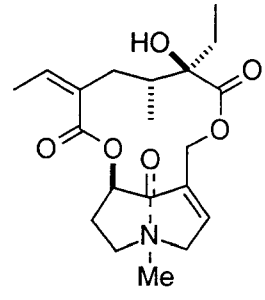
Lasiocarpine (**11**)



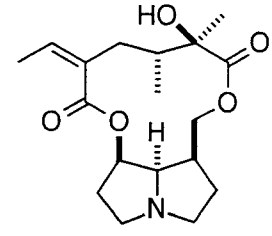
Retrorsine (**12**)



Monocrotaline (**13**)



Senkirkine (**14**)



Platyphylline (**15**)

The toxic effects of pyrrolizidine alkaloids are due to metabolites of the alkaloids and not the alkaloids themselves.[3,4] There are several possible pathways by which the alkaloids are metabolized (**Figure 1.1**).[3,4] In vivo hydrolysis of pyrrolizidine alkaloids leads to the formation of their necic acid and necine base moieties both of which are non-hepatotoxic.[20,30-31] The oxidation of pyrrolizidine alkaloids to their *N*-oxides is induced by hepatic microsomal enzymes.[4] The water soluble *N*-oxide metabolites are rapidly excreted in the urine.[32] The *N*-oxides themselves are much less toxic than the parent alkaloid, and can be regarded as detoxification products.[32-34] Finally, toxic pyrrolizidine alkaloids can be metabolized to pyrrolic derivatives (dehydroalkaloids) by a

hepatic P-450 monooxygenase.[33-34] These pyrrolic metabolites are believed to be responsible for the major toxic effects of pyrrolizidine alkaloids.[22]

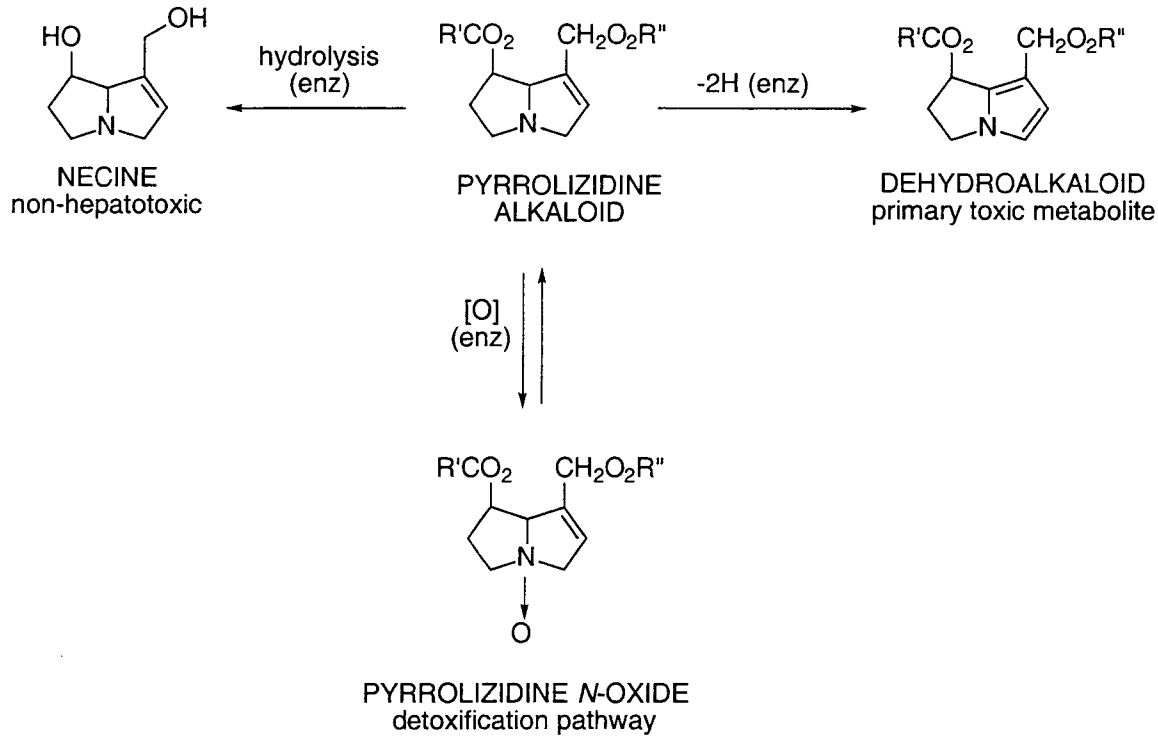


Figure 1.1. Major metabolic pathways of unsaturated pyrrolizidine alkaloids.[4]

As toxic primary metabolites, the pyrrolic derivatives of pyrrolizidine alkaloids are constitutionally dehydropyrrolizidine esters. These dehydropyrrolizidine esters are highly reactive compounds, in which the acyloxy substituents are activated by the pyrrole ring and become leaving groups. When an ester group is lost it leaves a positively charged dehydropyrrolizidine moiety which can react with nucleophilic species such as amines or thiols to form relatively stable alkylation products. Thus the dehydroalkaloids act effectively as bis alkylating agents (**Figure 1.2**).[22,32]

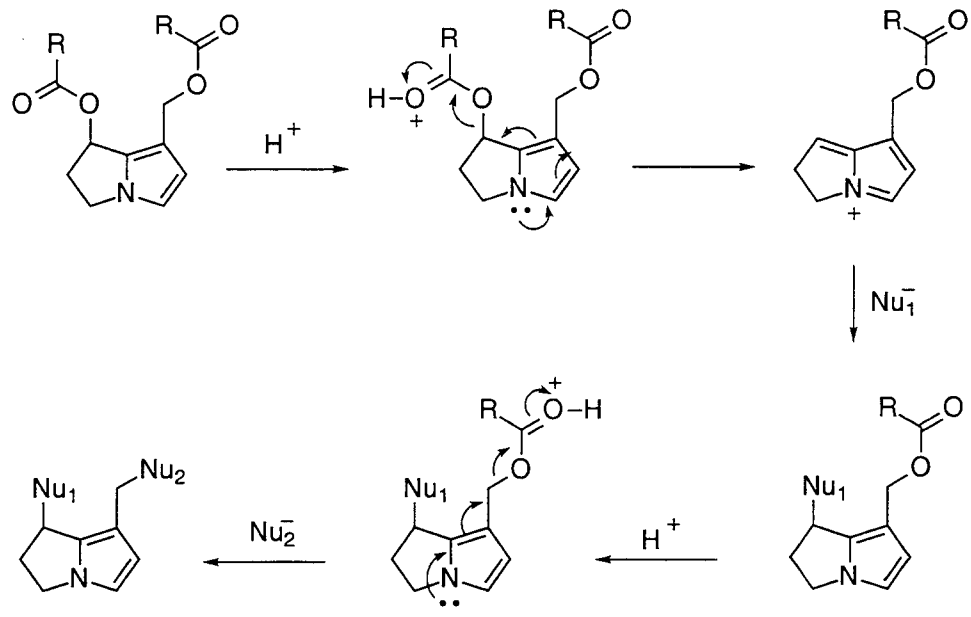


Figure 1.2. Mechanism of bisalkylation of pyrrolic derivatives of pyrrolizidine alkaloids.[32]

It is known that pyrrolizidine alkaloids are metabolized primarily in the liver, although small amounts of pyrrolic metabolites have been found in the lungs and kidneys. The hypothetical fate of a reactive pyrrolic metabolite in the liver is illustrated in **Figure 1.3**.[22] Some of the pyrrolic metabolites may be hydrolyzed while others might alkylate soluble thiols or amines, such as glutathione or amino acids. These relatively stable, soluble products will then be eliminated from the body. Some of these reactive pyrrolic metabolites may bind proteins or nucleic acids within the cell, and remain for a much longer time as "bound pyrroles". These "bound pyrroles" are believed to be responsible for toxic

effects in the cell. Some of the metabolites may survive long enough to be transported by the bloodstream to other organs such as the heart and lungs.[22]

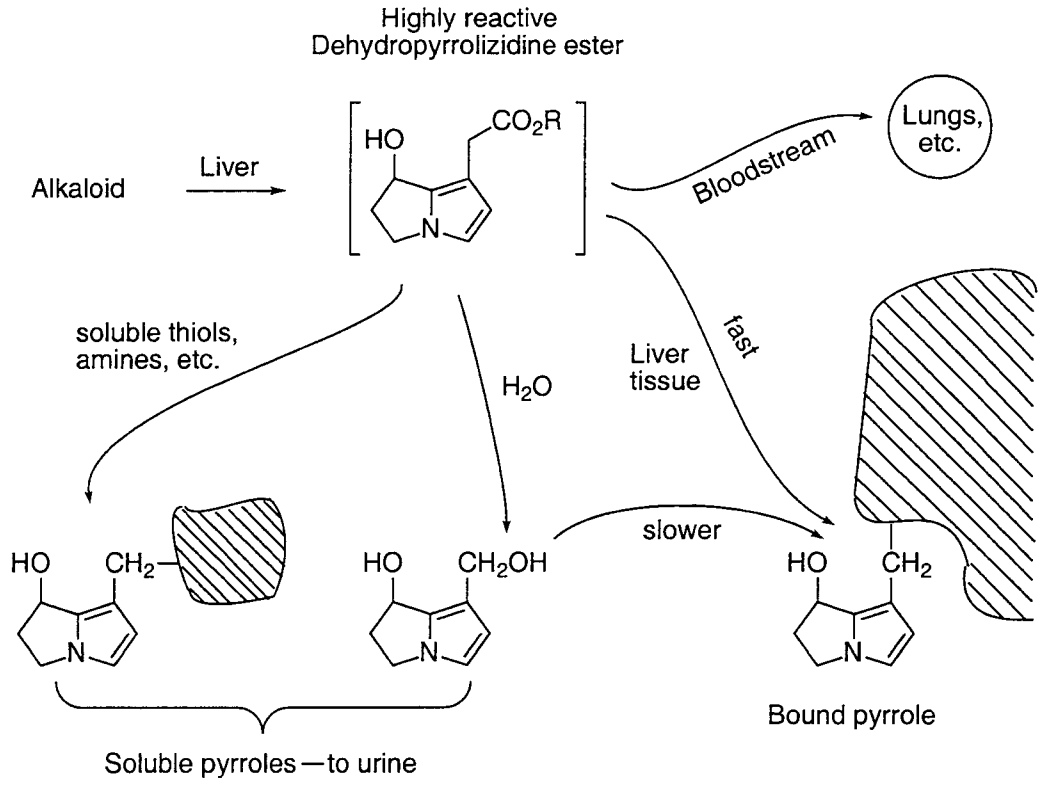
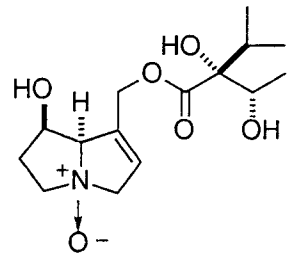


Figure 1.3. Hypothetical fate of a reactive pyrrolic metabolite (dehydropyrrolizidine ester) in the liver of a rat.[22]

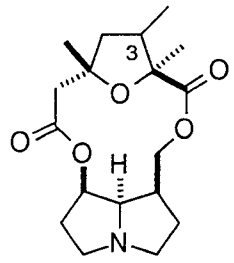
In addition to their toxicity, certain pyrrolizidine alkaloids, such as heliotrine (**10**), lasiocarpine (**11**), monocrotaline (**13**), and indicine *N*-oxide (**16**) have been found to have antitumor activity.[36,37] Indicine *N*-oxide (**16**) was tested in phase II clinical trials for the treatment of leukemia and solid tumors,[38-45] but its hepatotoxicity was found to be too high for its further development as an anticancer agent.



Indicine *N*-oxide (**16**)

Organic chemists have long been fascinated by the complex structural and synthetic puzzles posed by natural products and, like many natural products, pyrrolizidine alkaloids have presented challenging targets for synthesis. Synthetic routes have been devised for making necine bases and necic acids,[3] and a few of these have been extended to total synthesis of the ester alkaloids.[46-59] These syntheses not only have been valuable for establishing the precise structure and stereochemistry of many pyrrolizidine alkaloids, but also have been a valuable source of modified alkaloids or analogs with which to test structure-activity relationships and to study their metabolism and toxicity.[3]

Nemorensine (**1**) was isolated from three varieties of *Senecio nemorensis* L. including ssp. *Jacquinianus*, ssp. *fuchsii*, and var. *subdecurrens* GRISEB. by Klasek and coworkers in 1972.[1] Its structure was initially assigned as **17**, when another pyrrolizidine alkaloid retroisosenine (**18**) was isolated in 1975 from *Senecio nemorensis* L., var. *bulgaricus* (VEL.) STOJ. *et* STEF.[60] The configuration at C-3 in these two alkaloids was left unspecified.



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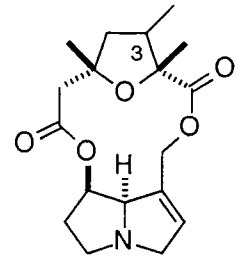
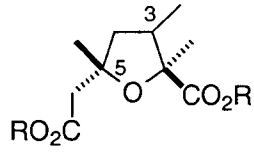
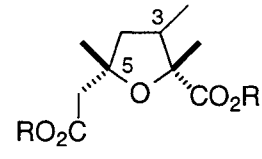


18

Alkaline hydrolysis of **17** and **18** gave necic acids **19** and **21** respectively. Although the structural features of necic acid **21** derived from **18** resemble those of the necic acid **19** from **17**, the actual values of chemical shifts in their ^{1}H NMR spectra are different. The necic acids **19** and **21** were converted to their dimethyl esters **20** and **22**, respectively, and the relative stereochemistry of the esters was assigned by assuming a deshielding effect by the methoxycarbonyl group at C-2 on the cis methyl protons at C-5. Since a downfield shift was observed for the methyl signal of the necic ester (**20**) derived from nemorensine relative to the corresponding signal in the necic ester (**22**) of retroisosenine, "nemorensic acid" was assigned as **19**. The structure of nemorensine was therefore represented by **17**. The necic acid from retroisosenine was assigned as **21** and the structure of the parent alkaloid was represented by **18**.[1,60]

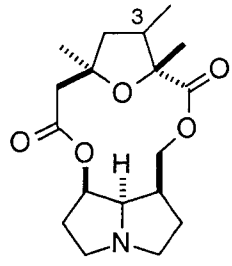


19 R = H
20 R = Me

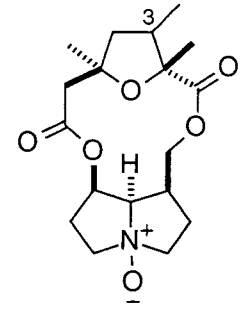


21 R = H
22 R = Me

Subsequently, the structure of nemorensine was revised without explanation to the stereoisomeric (2*R*,5*R*)-disubstituted tetrahydrofuran **23** when oxonemorensine (**24**), the *N*-oxide of **23**, was isolated in 1979.[61] Again, the configuration at C-3 was not specified in this structure.

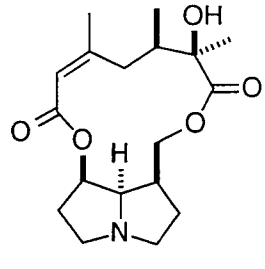


23



24

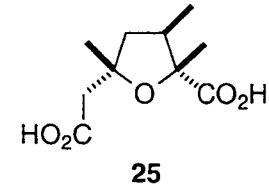
In related studies by Nghia[60] and Kirfel,[62] the necic acid **25** was shown to be present among the degradation products of both (-)-bulgarsenine (**26**) and (+)-doronenine (**27**). Thus, hydrolysis of (-)-bulgarsenine (**26**), isolated from *Senecio nemorensis* L., var. *bulgaricus* (VEL.) STOJ. *et* STEF., under both basic and acidic conditions, gave **25** resulting from cyclization of the intermediate 6-hydroxy α,β-unsaturated dicarboxylic acid (**Scheme 1**).[60]



(-)-Bulgarsenine (**26**)

KOH, MeOH or

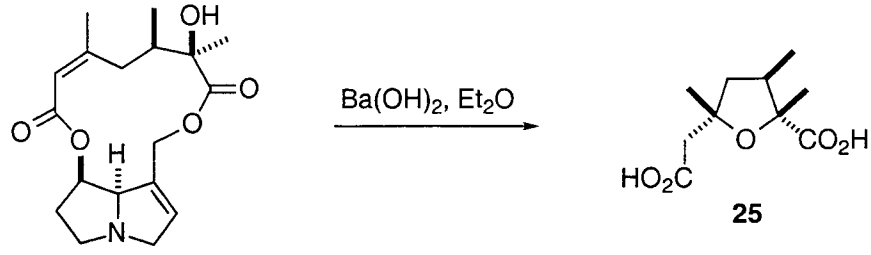
H_2SO_4, reflux



25

Scheme 1

The absolute configuration of (+)-doronenine (**27**) was determined by X-ray crystallographic analysis.[63] After basic hydrolysis, (+)-doronenine (**27**) was found to give the same necic acid **25** as obtained from bulgarsenine (**26**) (**Scheme 2**). The stereochemistry of this necic acid was determined by X-ray crystallographic analysis.[64]

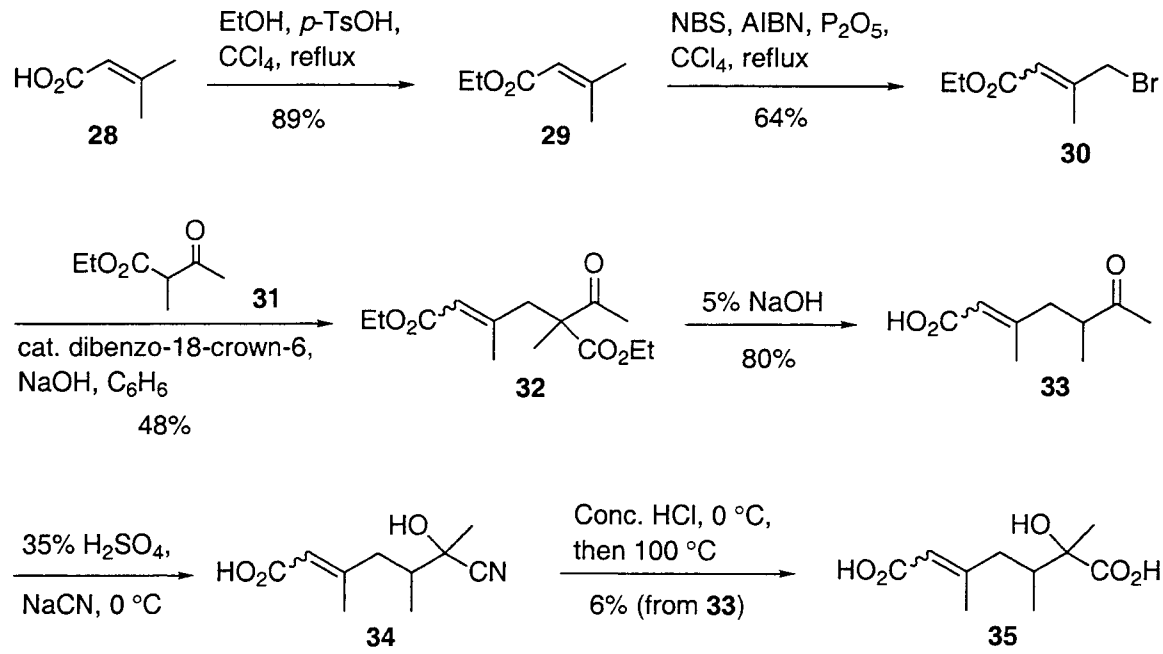


(+)-Doronenine (**27**)

25

Scheme 2

An open-chain form of nemorensic acid (**35**), isolated from the acidic fraction of an ethereal extract of *Senecio nemorensis* L., was first synthesized by Röder as a racemate in 1979.[65] The synthesis started from commercially available 3,3-dimethylacrylic acid (**28**). Esterification of **28** gave **29**, which was reacted with *N*-bromosuccinimide (NBS) to afford a mixture of *cis*- and *trans* bromo esters **30** in a 1:1 ratio. The mixture **30** was alkylated with ethyl α-methylacetoacetate (**31**) in the presence of dibenzo-18-crown-6 as catalyst to yield keto ester **32** as the coupled product. Saponification of **32** with sodium hydroxide was followed by spontaneous decarboxylation of the β keto acid to furnish keto acid **33**. After formation of the cyanohydrin **34**, the latter was treated with concentrated hydrochloric acid at high temperature to produce a dicarboxylic acid **35** presumably as a mixture of stereoisomers (**Scheme 3**).[65]

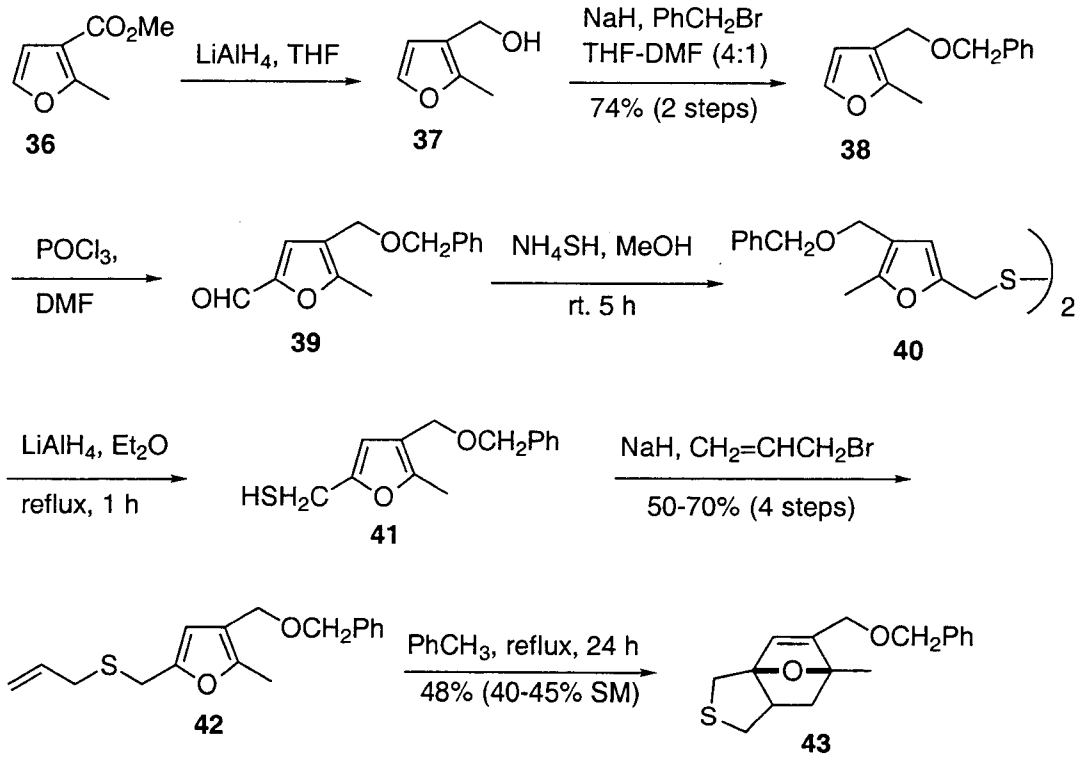


Scheme 3

In 1985, Klein reported the first synthesis of (±)-**25**, which he claimed to be the racemate of the necic acid of retroisosenine (**18**).[66] This claim was later proved to be incorrect, and Klein's product was shown to be the necic acid of nemorensine by an asymmetric synthesis of (+)-**25** from this laboratory.[67] In Klein's synthesis, an intramolecular Diels-Alder reaction of furfuryl allyl sulfide **42** was the key step used for the construction of the tetrahydrofuran ring system.

The Klein synthesis of **25** began from commercially available methyl 2-methyl-3-furancarboxylate (**36**), which was reduced to its corresponding alcohol **37** with lithium aluminum hydride. Subsequent benzylation of the primary alcohol gave benzyl ether **38**. Vilsmeier formylation of **38** occurred exclusively at the C-5 position to produce **39**, which was treated with ammonium hydrogen sulfide to yield the crude furfuryl disulfide **40**. Without purification, this disulfide was immediately reduced with lithium aluminum hydride to the mercaptan **41**, which was directly reacted with allyl bromide to afford allyl sulfide **42**. With this key

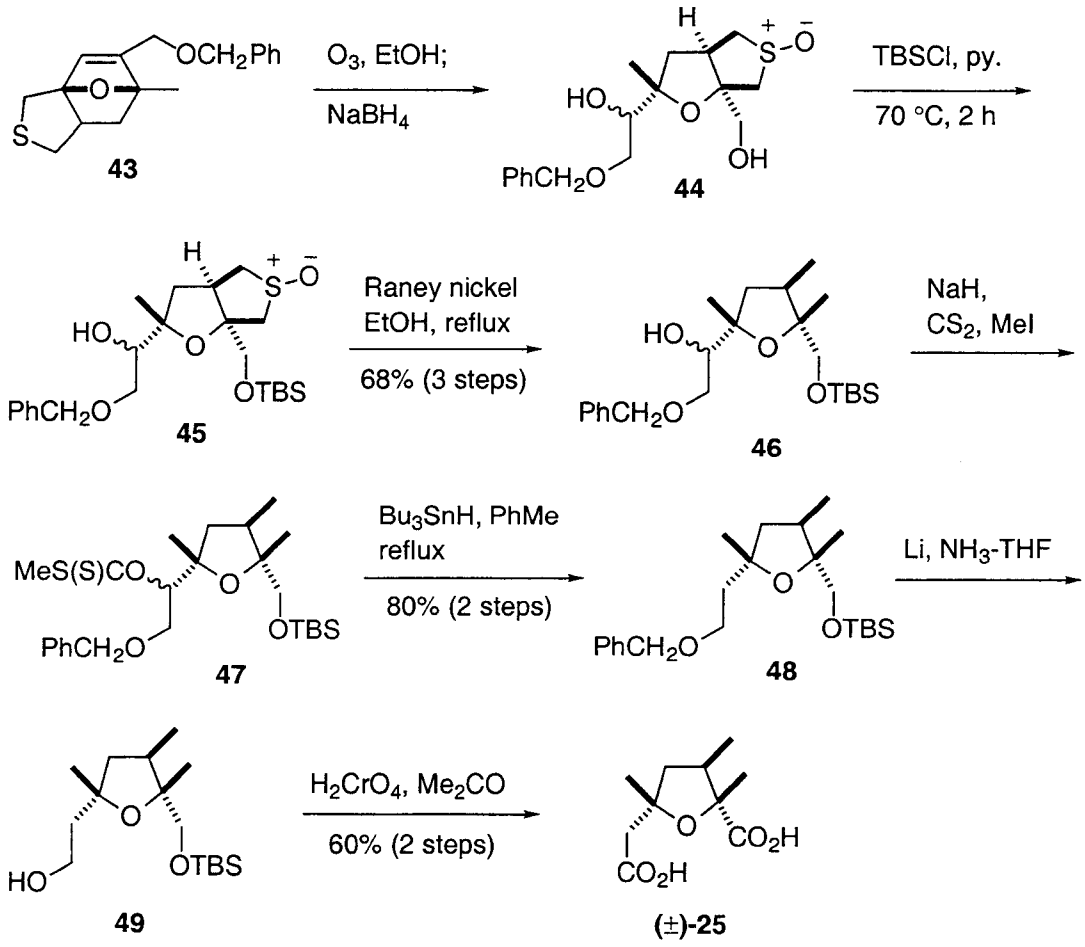
intermediate in hand, an intramolecular Diels-Alder reaction was effected in refluxing toluene to produce the desired cycloadduct **43** in 48% yield along with 40-45% of recovered starting material. This cycloaddition was shown to be an equilibrium process since the same ratio was obtained when either isolated product **43** or starting material **42** was resubmitted to the reaction conditions (**Scheme 4**).[66]



Scheme 4

Ozonolysis of **43**, followed by a reductive workup using sodium borohydride, yielded the tetrahydrofuran **44** (**Scheme 5**). This dihydroxy sulfoxide was produced as a mixture of diastereomers, which was used in subsequent reactions without separation. The primary alcohol of **44** was

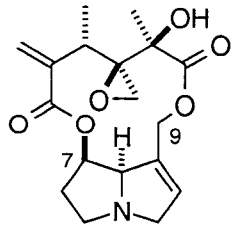
selectively silylated in the presence of the secondary alcohol with *tert*-butyldimethylsilyl chloride (TBSCl) in pyridine at elevated temperature to afford **45**, which was treated with Raney nickel in refluxing ethanol. This served to reduce the sulfoxide and desulfurize the resultant cyclic sulfide to yield the trimethyl substituted tetrahydrofuran **46**. Removal of the secondary hydroxyl group of **46** proceeded cleanly using Barton's two-step method, in which the crude xanthates **47** were reduced with tri-*n*-butyltin hydride in refluxing toluene. The benzyl protecting group of **48** was removed with lithium in ammonia, and the resultant alcohol **49** upon oxidation with Jones' reagent directly afforded (±)-**25**.[66]



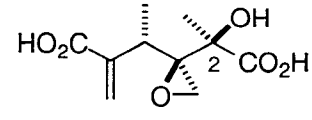
Scheme 5

In Klein's (±)-**25**, the methyl groups at C-2 and C-5 are in a *cis* orientation, which agrees with the assignment made to the necic acid of retroisosenine (**18**).[60] It was therefore presumed that (±)-**25** is the necic acid of retroisosenine (**18**). However, the first asymmetric synthesis of (+)-**25** accomplished in this laboratory has shown that this dicarboxylic acid is not the necic acid of retroisosenine, but rather is the necic acid of nemorensine (**1**).[67] In addition, the synthesis of (+)-**25** has necessitated revision of the stereochemistry of nemorensine and has established the absolute configuration of the necic acid of this alkaloid.[67]

(-)-Swazine (**2**) was isolated from an extract of *Senecio swaziensis* Compton obtained in Swaziland, South Africa.[2] Swazine was found to be one of the more complex structures among the dilactone pyrrolizidine alkaloids, consisting of a fully functionalized dicarboxylic acid derivative **50** (swazinecic acid) which bridges the C-7 and C-9 hydroxyl groups of retronecine to form a twelve-membered dilactone.



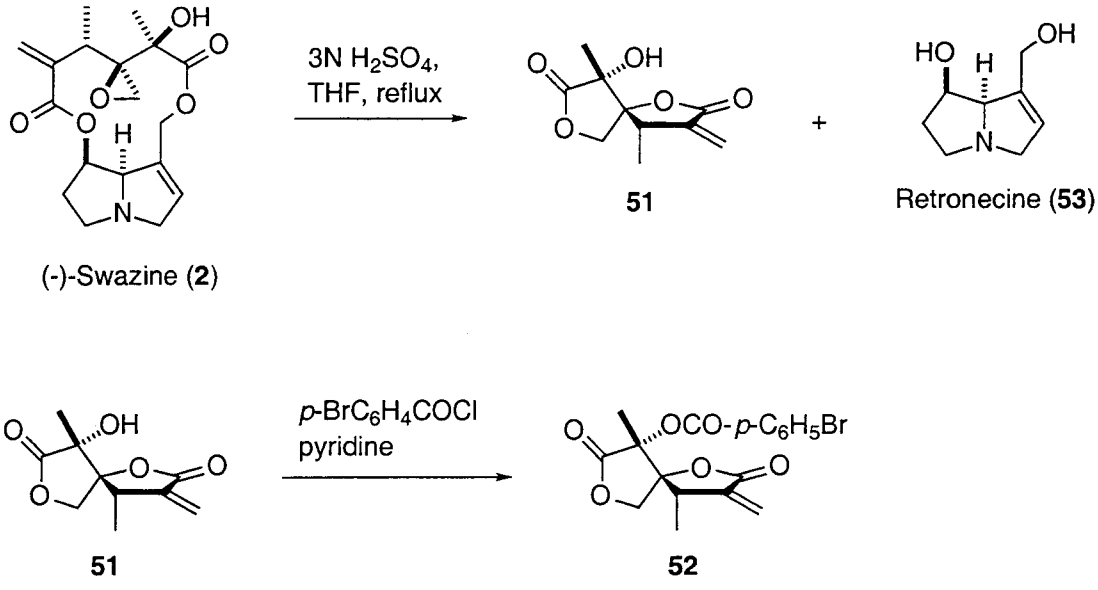
(-)-Swazine (**2**)



Swazinecic acid (**50**)

Neither acidic nor careful basic hydrolysis of **2** has permitted isolation of swazinecic acid (**50**).[2,68] Instead, the constitution of this necic acid was inferred from the spirodilactone **51** obtained upon treatment of (-)-swazine (**2**) with hot, 3N

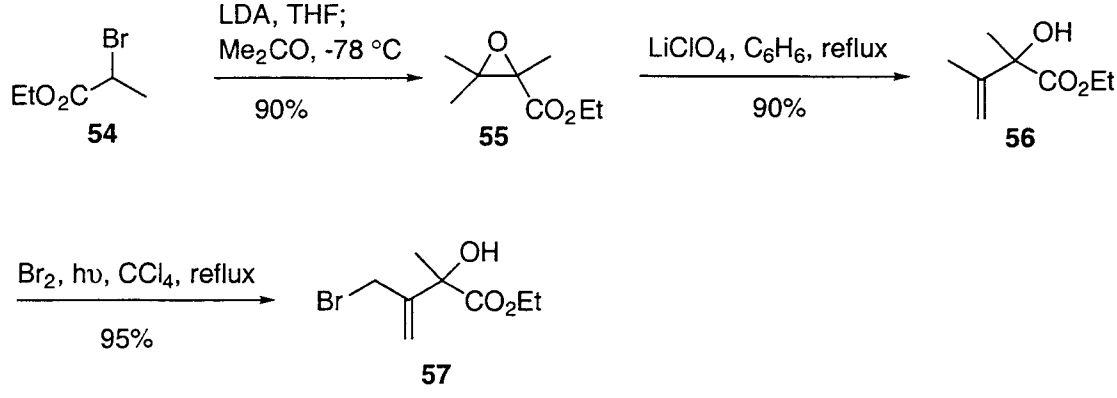
sulfuric acid (**Scheme 6**). The structure of **51** was established by X-ray crystallographic analysis of its *p*-bromobenzoate **52**.[2]



Scheme 6

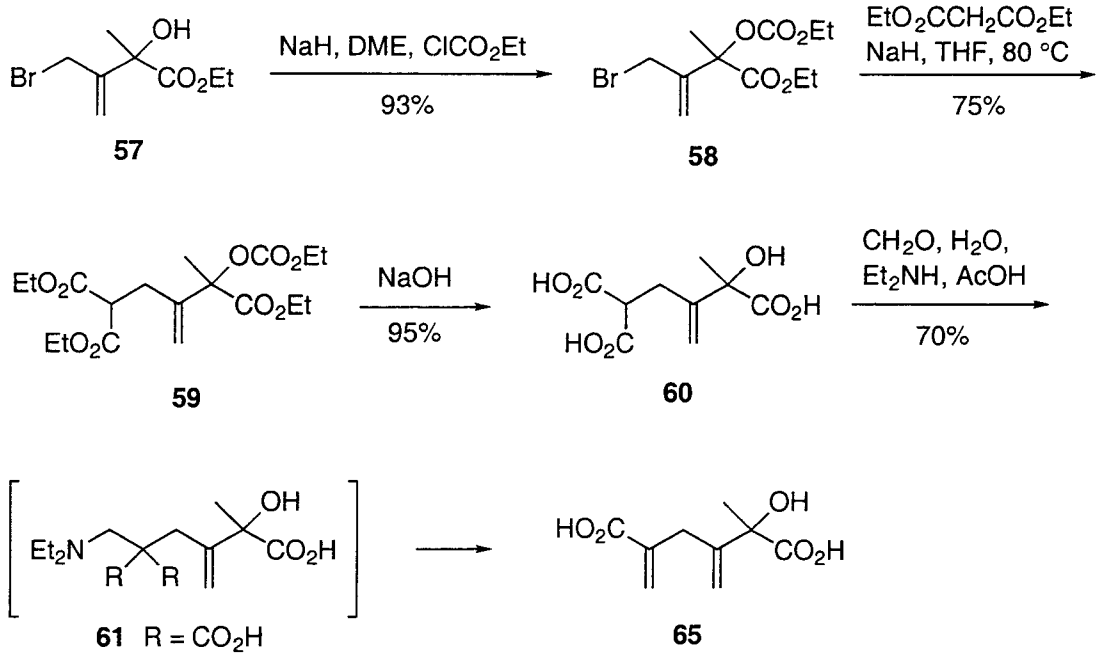
Initially, swazine was formulated as the dilactone isomeric with **2**, in which swazinecic acid (**50**) was connected to retronecine in the reverse orientation.[2] This assignment was subsequently revised, and the revision was accepted after a more complete degradative and spectroscopic investigation of the alkaloid.[68,69] The latter study also led to the absolute configuration for (-)-swazine represented by **2**. Although evidence for this stereostructure seemed persuasive, we nevertheless felt that before attempting a synthesis of **2**, it was prudent to verify the assignment made to swazinecic acid, particularly in view of the harsh conditions under which the relationship between stereocenters in **50** and its derived spirodilactone **51** had been deduced.

Gordon-Gray and Whiteley had previously attempted to synthesize spirodilactone **51**. Synthesis of the intermediate dicarboxylic acid **65** was accomplished by either condensation of diethyl malonate with **58**, or a coupling reaction of **62** with cuprate **63**. The first synthesis started with the Darzens condensation of α-bromo ester **54** with acetone to afford glycidic ester **55**, which underwent elimination to allylic hydroxy ester **56**. Resolution of **56** was attempted in order to accomplish an absolute stereoselective synthesis of spirodilactone **51** but was unsuccessful. The synthesis, continued in racemic form, next involved allylic bromination of **56** to give bromo ester **57** (**Scheme 7**).[70]



Scheme 7

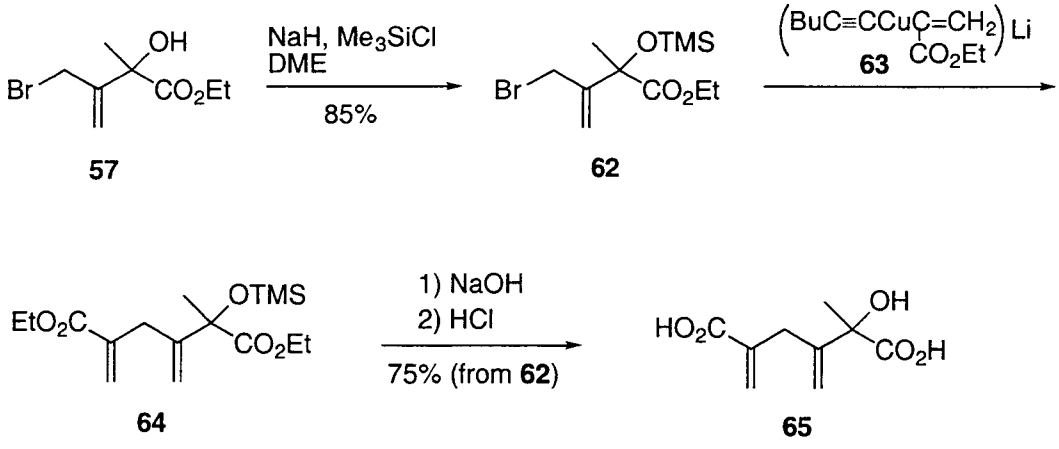
The tertiary alcohol of **57** was protected as its *O*-ethoxycarbonyl derivative **58**, and the latter was condensed with diethyl malonate to furnish **59**. Hydrolysis of **59** produced the triacid **60** which, after stirring with the Mannich reagent prepared from aqueous formaldehyde, diethylamine, and a buffered acetic acid solution gave the diacid **65** (**Scheme 8**).[70]



57 **58** **59** **60** **61** R = CO_2H **65**

Scheme 8

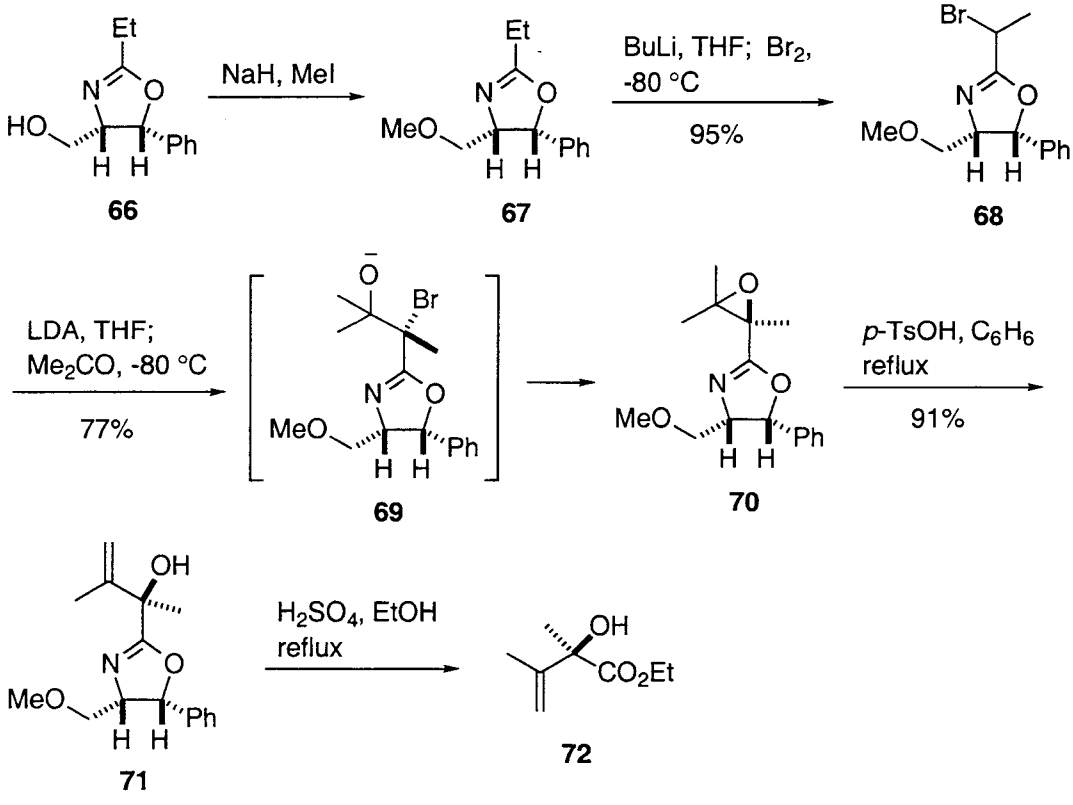
A more convergent at synthesis of **65** was accomplished by a coupling reaction of **62** with the cuprate **63** to provide diester **64**, which on hydrolysis yielded the diacid **65** (**Scheme 9**). Again, all attempts at resolution of this dicarboxylic acid failed.[70]



57 **62** **64** **65**

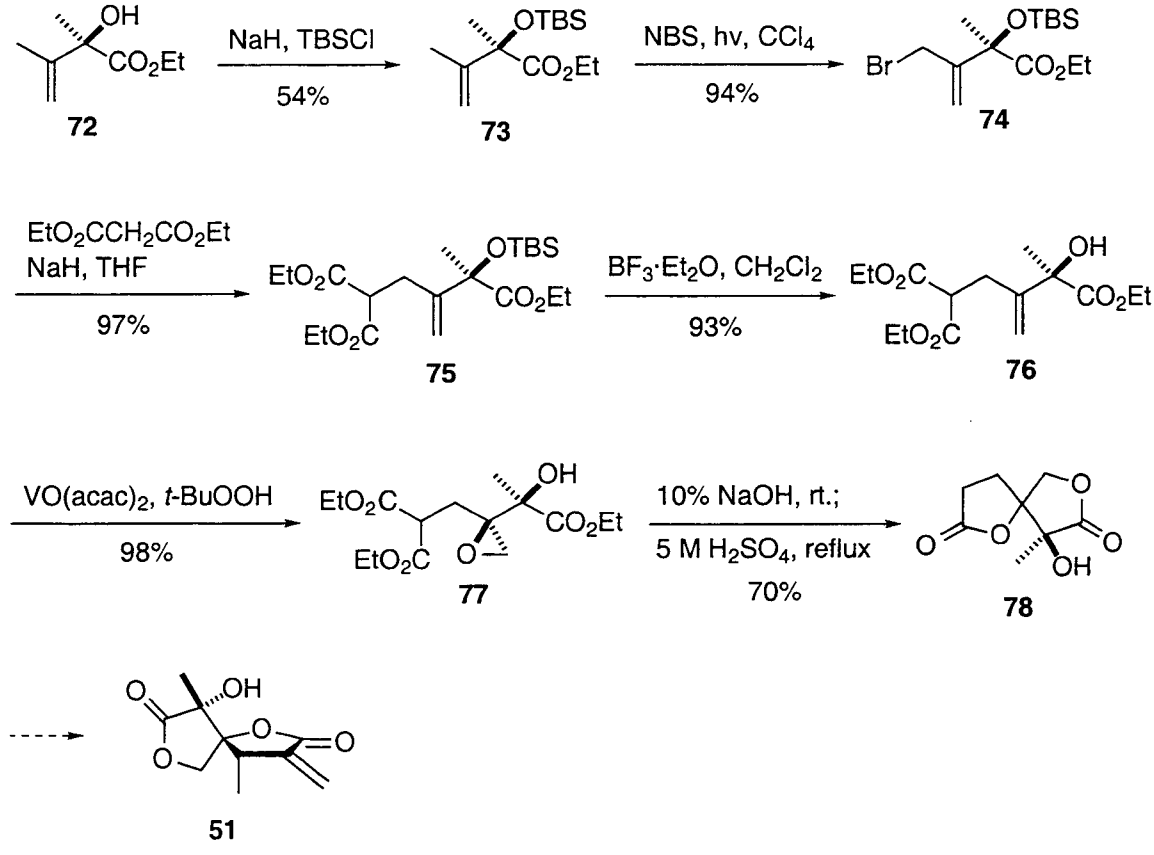
Scheme 9

Subsequently, an asymmetric synthesis of spirodilactone **51** was attempted by Whiteley.[71] The commercially available oxazoline **66** was first converted into its methyl ether **67** which was then brominated to afford **68** as a mixture of diastereoisomeric bromides (**Scheme 10**). Deprotonation of **68** using lithium diisopropylamide as base afforded the lithiooxazoline with the halogen atom anti to the lithium cation as the presumed thermodynamically favored form. The α-anion, as expected, attacked the carbonyl group of acetone from the least hindered face; this was followed by spontaneous S_N2 displacement of the halogen in **69** to form the desired epoxy oxazoline **70** with the required (*R*)-configuration at the α-carbon. In the presence of excess *p*-toluenesulfonic acid, epoxide **70** was rearranged to allylic alcohol **71**, which underwent subsequent hydrolysis to produce α-hydroxy ester **72**.



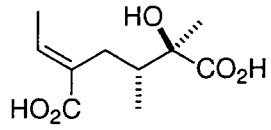
Scheme 10

The hydroxyl group of **72** was protected as its *tert*-butyldimethylsilyl (TBS) ether **73**, and this was followed by a photolytic bromination using *N*-bromosuccinimide to produce allylic bromide **74**. Coupling of **74** with diethyl malonate anion gave the triester **75**, from which the silyl group was removed with boron trifluoride etherate in dichloromethane to provide alcohol **76**. Vanadium-catalyzed epoxidation of allylic alcohol **76** with *tert*-butylhydroperoxide as the epoxidizing agent afforded the required *erythro* isomer **77** (**Scheme 11**).[71] Basic hydrolysis of triester **77** with sodium hydroxide followed by refluxing in sulfuric acid afforded spirodilactone **78**. Although work is reported to be in progress to convert **78** into spirodilactone **51**,[71] no synthesis of **51** has yet been disclosed.

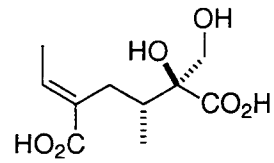


Scheme 11

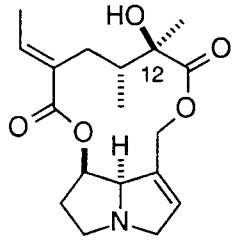
As part of a program directed towards the synthesis of dilactone pyrrolizidine alkaloids, a general approach to assembling the necic acid portion of these natural products from terpenoid precursors has been devised in this laboratory.[47-49] The first two necic acids synthesized by this strategy, integerrinecic acid (**79**)[46,47] and usaraminecic acid (**80**),[48] led to the stereoselective synthesis of their parent alkaloids (-)-integerrimine (**81**) and (+)-usaramine (**82**).[49]



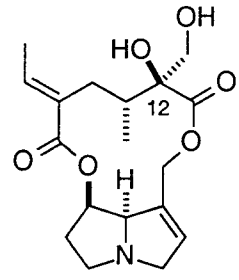
Integerrinecic acid (**79**)



Usaraminecic acid (**80**)



(-)-Integerrimine (**81**)

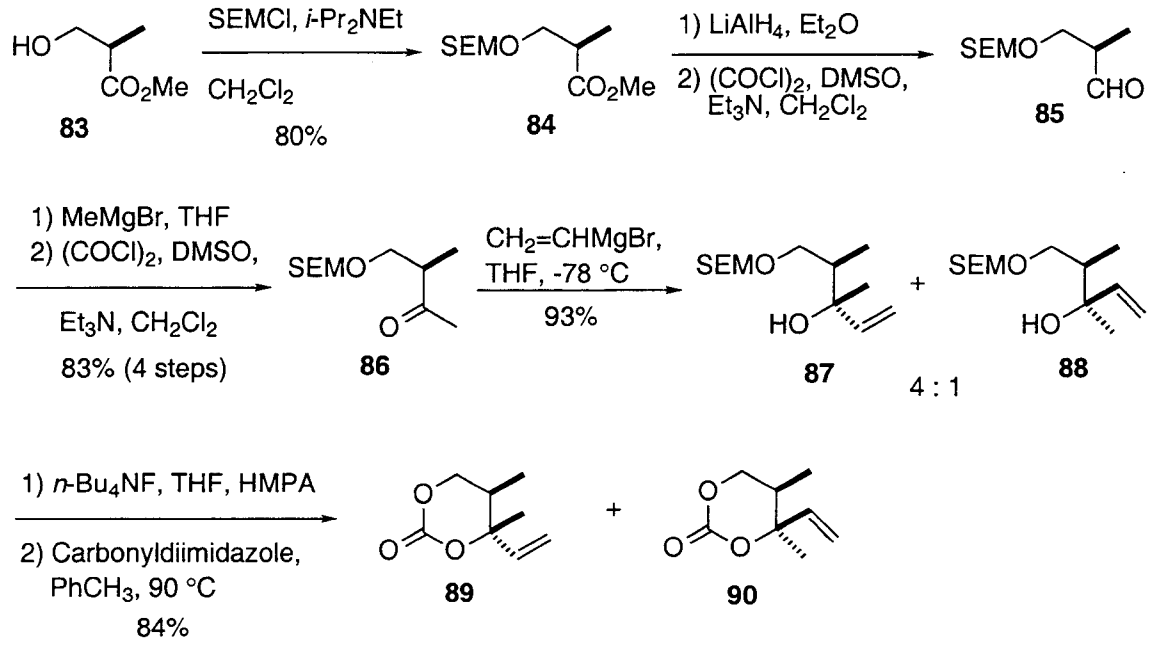


(+)-Usaramine (**82**)

Two routes to integerriminecic acid (**79**) were completed by White et al. The first, starting from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate (**83**) led in nineteen steps to integerrinecic acid lactone (**98**) which was transformed to the necic acid derivative **100**.[46,49] A second, shorter synthesis of **98** was accomplished starting from (*R*)-(+)-citronellal (**102**).[47,49]

In the first synthesis of **79**, initial protection of **83** with [2-(trimethylsilyl)ethoxy]methyl (SEM) chloride in the presence of

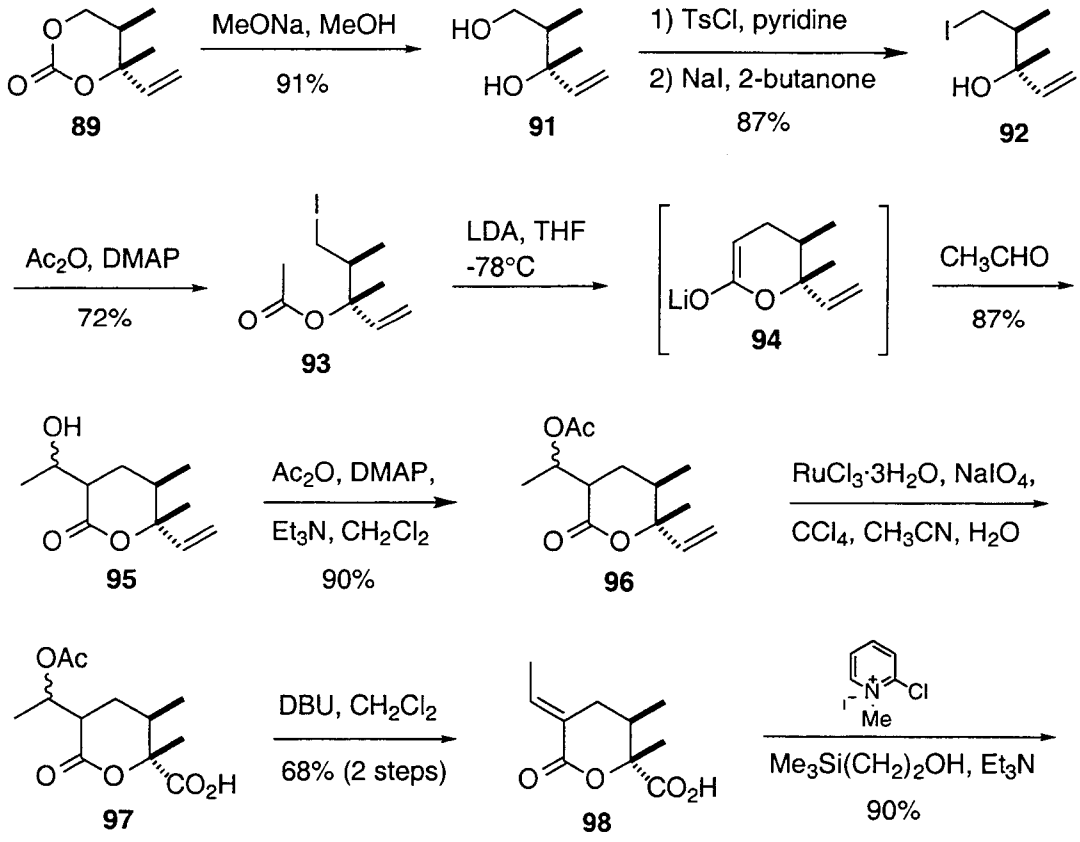
diisopropylethylamine afforded the ether **84** (**Scheme 12**). The ester function in **84** was reduced with lithium aluminum hydride, and the resultant alcohol was oxidized to aldehyde **85** under Swern's conditions. Transformation of **85** to methyl ketone **86** was accomplished by treatment with methylmagnesium bromide, followed by Swern oxidation of the resultant alcohol. A chelation-controlled addition of vinylmagnesium bromide to ketone of **86** yielded a 4:1 mixture of the desired alcohol **87** and its diastereomer **88**, respectively. Without separation, these diastereomers were converted to their cyclic carbonates **89** and **90** by exposure to tetra-*n*-butylammonium fluoride in hexamethylphosphoramide, followed by treatment of the resultant diols with carbonyldiimidazole.[46,49]

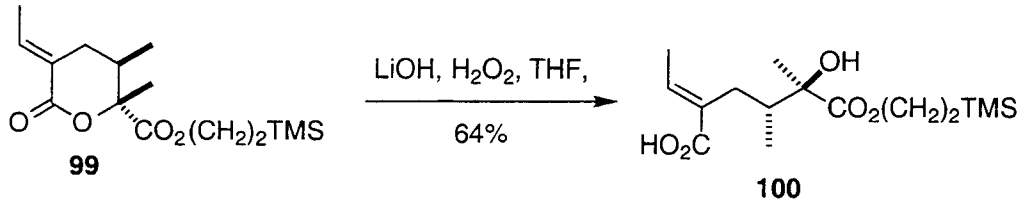


Scheme 12

The major carbonate **89** was separated and was transformed to integerrinecic acid lactone **98** in nine steps (**Scheme 13**). Thus, selective

conversion of **89** to the primary tosylate and then to iodide **92**, was followed by acetylation to furnish iodo acetate **93**. Intramolecular alkylation was accomplished by exposure of **93** to excess lithium diisopropylamide, and the resultant enolate **94** was immediately treated with acetaldehyde to provide the aldol product **95**. Acetylation of this mixture of diastereomeric β-hydroxy lactones gave a mixture of acetates **96**, which was cleaved oxidatively with sodium periodate in the presence of a catalytic amount of ruthenium(III) chloride trihydrate, to yield a mixture of the corresponding carboxylic acids **97**. The pair of acids **97** was smoothly converted into lactone **98** upon exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The carboxylic acid function in lactone **98** was protected as its (trimethylsilyl)ethyl ester **99** which was selectively hydrolyzed to the integerrinecic acid derivative **100**.[46,49]

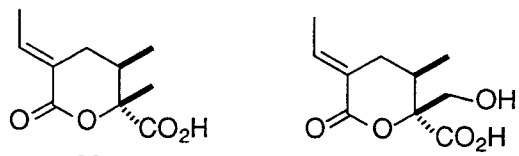




99 **100**

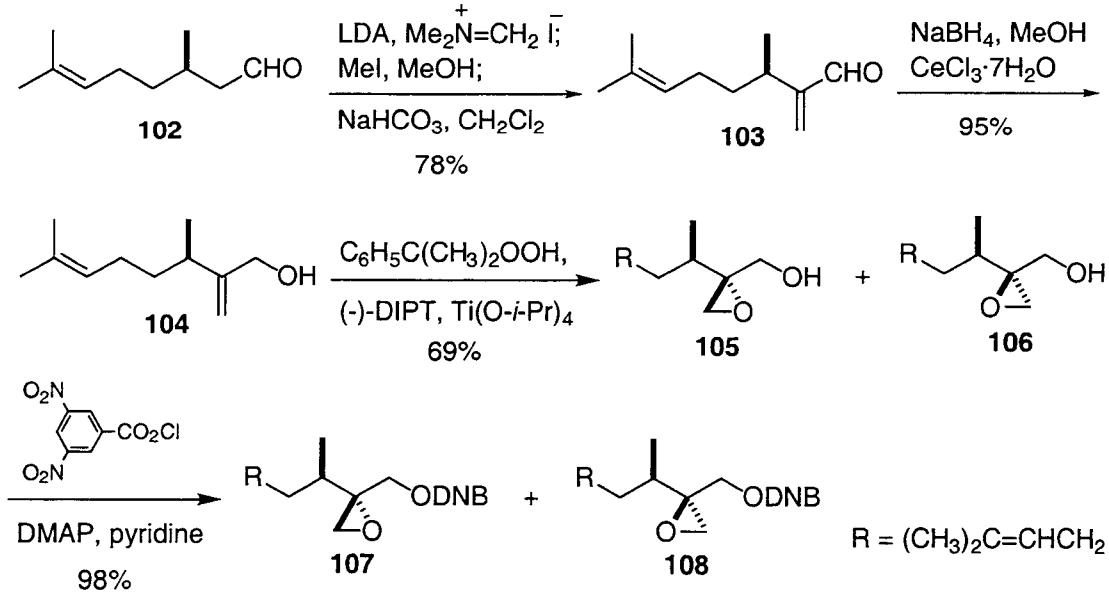
Scheme 13

After completion of the synthesis of integerrimine (**81**), a search began for a general route to necic acids which could accommodate additional functional groups such as that present in usaramine (**82**). The initial goal therefore became a stereoselective pathway leading to both lactones **98** and **101** from a common intermediate. Comparison of **98** and **101** suggested that the methyl and hydroxymethyl substituents of these δ-lactones could be installed by either hydride or alkoxide addition to a terminal epoxide, respectively. This strategy necessitated a change in the original synthetic plan departing from **83**, whilst retaining the requirement for a progenitor from the chiral pool that would provide the (3*R*) methyl substituent of the necic acids. (*R*)-(+)-Citronellal (**102**) seemed ideally suited for this purpose, and all of the subsequent approaches to necic acids employed this monoterpene as the starting material.[47,49]



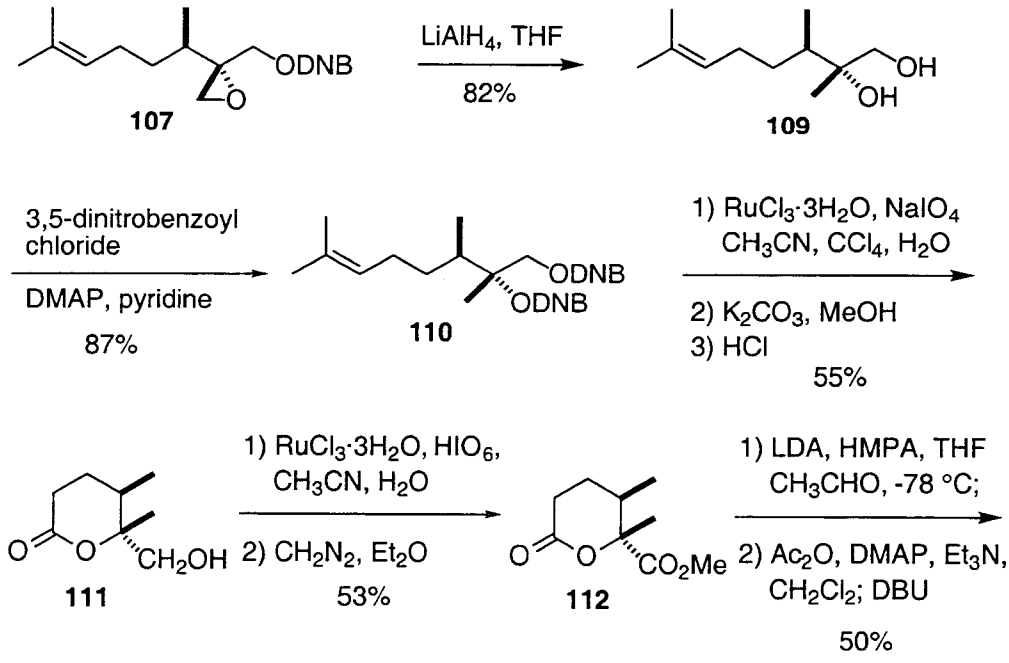
98 **101**

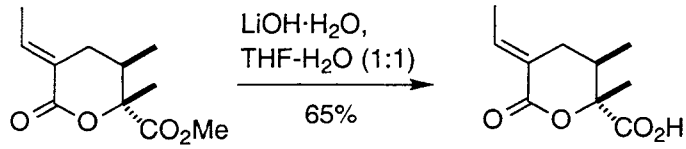
Alkylation of the lithium enolate derived from **102** with Eschenmoser's salt, followed by methylation of the resulting amine and treatment with aqueous sodium bicarbonate, gave the acrolein derivative **103**. Selective carbonyl reduction of the unsaturated aldehyde **103** occurred smoothly with sodium borohydride in the presence of cerium chloride and provided the allylic alcohol **104**. It was expected that Katsuki-Sharpless catalytic asymmetric epoxidation of **104** employing titanium(IV) isopropoxide and diisopropyl (-)-tartrate would afford the (*R*) epoxide **105** in high diastereomeric excess but in fact a 3:1 mixture of **105** and the diastereomeric epoxide **106** was obtained. The preexisting asymmetric center in **104** apparently exerts a steric bias on the epoxidation which results in a substrate-catalyst mismatch and consequent poor stereoselectivity. Support for this postulate was obtained by epoxidation of **104** with the enantiomeric (*matched*) (+)-tartrate, which yielded diastereoisomers **105** and **106** in a ratio of 4:96, respectively. The mixture of epoxy alcohols **105** and **106** were converted to their separable, crystalline 3,5-dinitrobenzoates **107** and **108** (**Scheme 14**).[47,49]



Scheme 14

With pure **107** in hand, attention was turned to its conversion into lactone **98** (**Scheme 15**). Reduction of **107** with lithium aluminum hydride afforded the diol **109**, which was protected as its bis-3,5-dinitrobenzoate derivative **110**. Oxidative scission of the isopropylidene group of **110** was accomplished with catalytic ruthenium trichloride and sodium metaperiodate. Subsequent methanolysis of the 3,5-dinitrobenzoate esters, followed by acid-catalyzed lactonization, provided **111**. Oxidation of **111** with a catalytic amount of ruthenium(III) chloride and periodic acid, followed by esterification of the resulting crude carboxylic acid , gave methyl ester **112**. The lithium enolate derived from **112** was condensed with acetaldehyde, and the resultant aldol product was acetylated. Elimination of acetic acid with DBU gave (*E*)-lactone **113** and subsequent hydrolysis with lithium hydroxide furnished (+)-**98**. Since synthesis of the integerrinecic acid derivative **100** had been accomplished previously (see **Scheme 13**), this route constitutes a second, enantioselective pathway to the necic acid.[47,49]

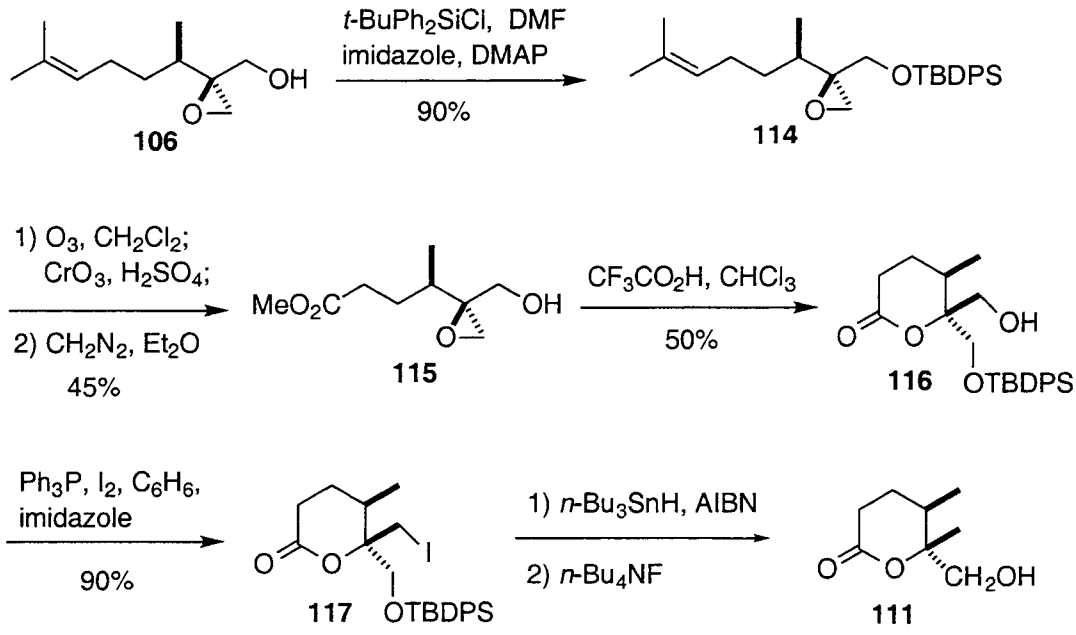




113 **98**

Scheme 15

The synthetic route from (*R*)-(+)-citronellal to integerrinecic acid lactone **98** described above is unfortunately marred by poor diastereoselectivity in the Katsuki-Sharpless epoxidation as compared to that observed in related systems.[47,49] Recognizing that the stereochemical efficiency of this approach would be enhanced if epoxide **106**, resulting from a *matched* substrate-catalyst reaction, were employed, a modification of the pathway was devised whereby **111** could be accessed from this isomer (**Scheme 16**). Transformation of **106** to **111** effectively required inversion of the quaternary center, a process which, in principle, could be accomplished by epoxide opening with attack by an internal carboxyl function. The primary alcohol of **106** was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether **114** before oxidative cleavage of the olefin was carried out with ozone. Workup using Jones' reagent afforded a carboxylic acid which was esterified to give **115**. Upon treatment of **115** with trifluoroacetic acid a single hydroxy lactone **116** was produced in which epoxide opening had occurred with inversion at the quaternary carbon center. The primary alcohol **116** was converted to its iodide **117**, which underwent reduction upon treatment with tri-*n*-butyltin hydride. Removal of the *tert*-butyldiphenylsilyl ether then yielded **111**,[47,49] bringing this route into convergence with that shown in **Scheme 15**.

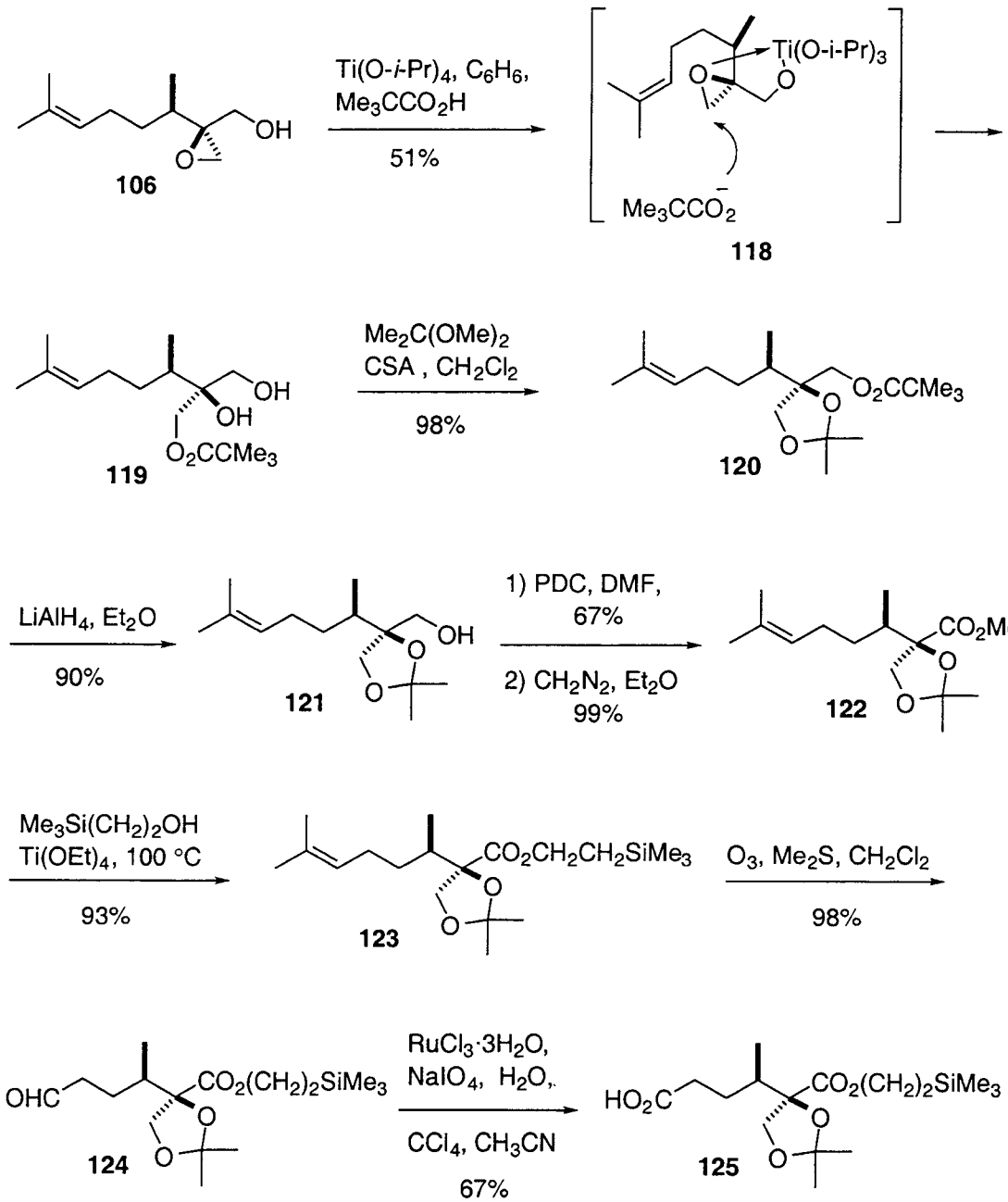


Scheme 16

The structure of (+)-usaramine (**82**) differs from that of (-)-integerrimine (**81**) only in the presence of a hydroxymethyl substituent in place of the methyl group at C-12. In planning an approach to the necic acid portion of **82**, the objective was to employ the same epoxide(s) that had been used for the synthesis of **82**. In this case, however, hydrolytic rather than reductive opening of the epoxide function was required.[48-49]

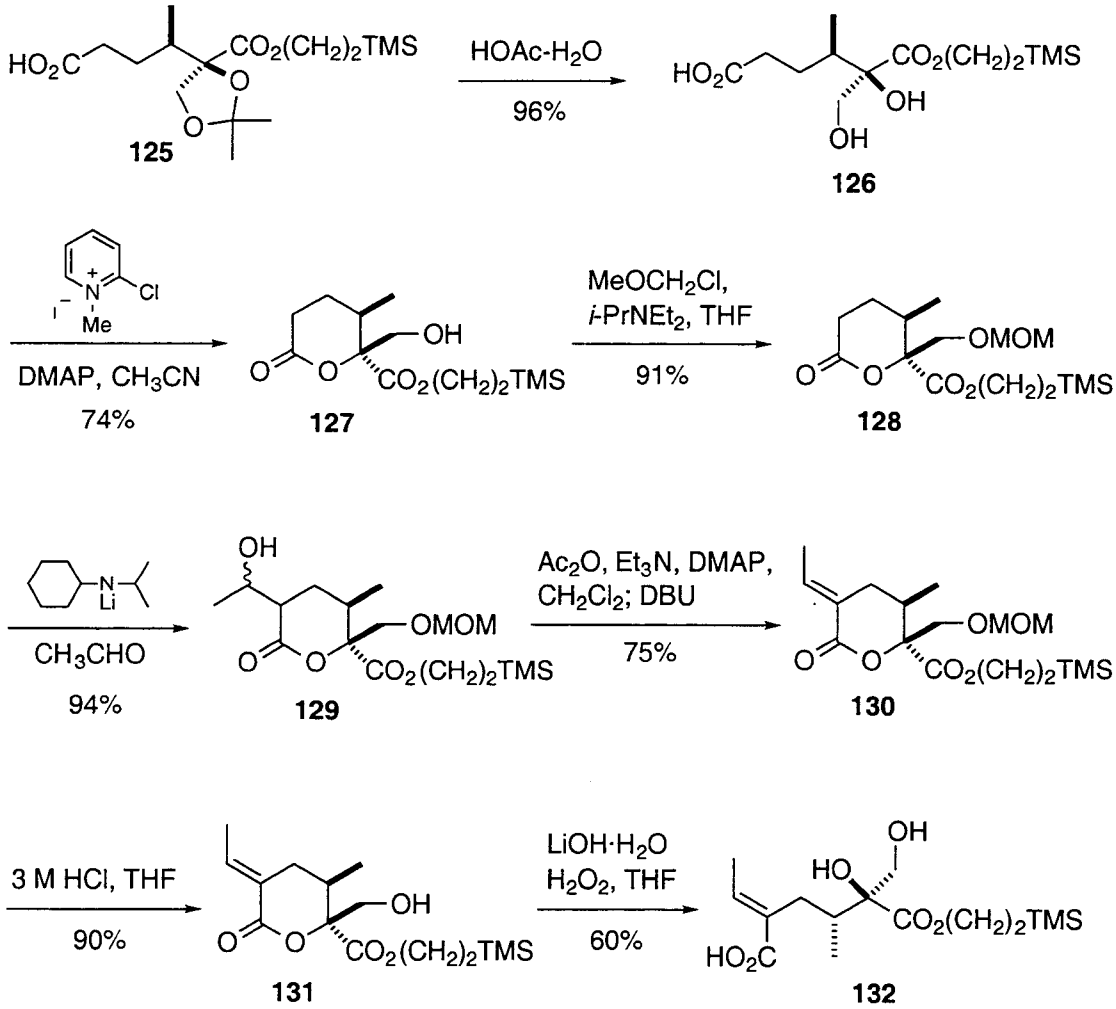
Epoxide **106**, prepared in high diastereoselective excess *via* the epoxidation procedure described previously, was subjected to titanium isopropoxide-mediated ring opening in the presence of pivalic acid (**Scheme 17**). Nucleophilic attack occurred *via* **118** at the more accessible methylene carbon to afford pivalate **119**. The diol function was protected as the acetonide **120**, and reduction of the latter to **121** followed by oxidation with pyridinium dichromate (PDC), led to an unstable carboxylic acid which was isolated as its methyl ester **122**. Transesterification of **122** to the (trimethylsilyl)ethoxylmethyl (SEM) ester

123 was achieved using titanium(IV) ethoxide as catalyst in a modification of the method reported by Seebach.[72] Cleavage of the isopropylidene group of **123** occurred cleanly upon ozonolysis to yield aldehyde **124**, and oxidation of this material afforded the truncated carboxylic acid **125**.[48-49]



Scheme 17

Hydrolysis of the acetonide **125** gave the dihydroxy acid **126**, which was lactonized with Mukaiyama's reagent to provide δ-lactone **127**. After protection of **127** as its methoxymethyl (MOM) ether, condensation of the enolate derived from **128** with acetaldehyde, followed by acetylation and elimination of acetic acid from the resulting β-acetoxy lactone, gave the (*E*)-olefin **130**. Hydrolysis of **130** to the usaraminecic acid derivative **130** was carried out, first with mineral acid to remove the MOM ether and then with basic peroxide to open the lactone of **132** (**Scheme 18**).[48-49]



Scheme 18

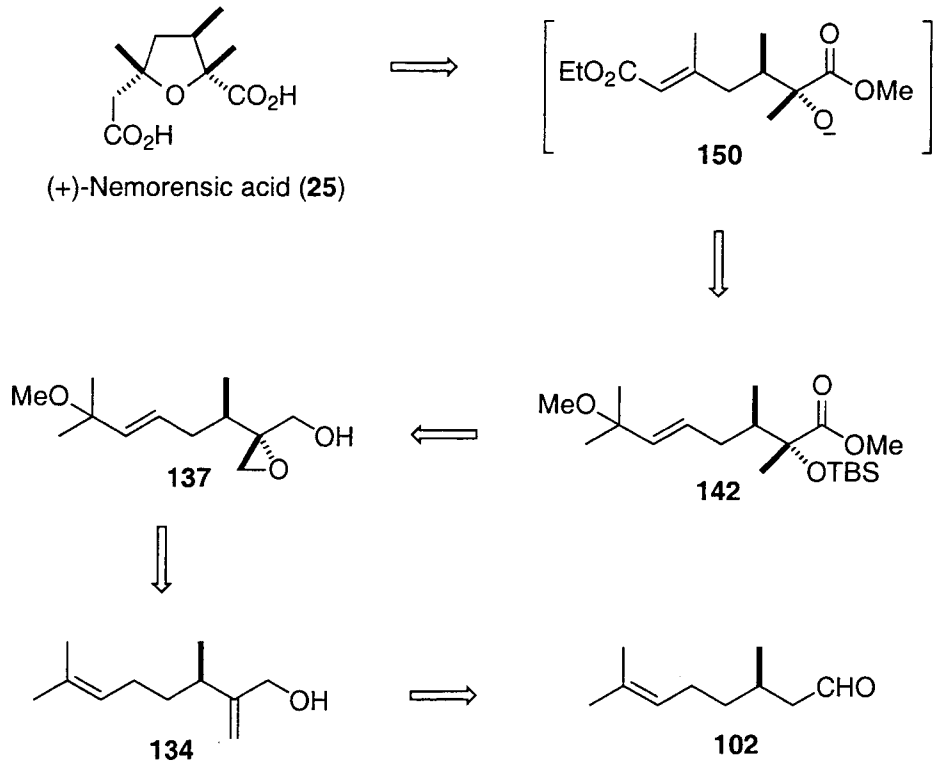
The foregoing studies provide a firm foundation on which to base further advances in the synthesis of necic acids. The chapters which follow describe two examples of the terpenoid route to necic acids which illustrate the power of this approach. The first example, an asymmetric synthesis of (+)-nemorensic acid, applies (*R*)-(+)-citronellal to the construction of a heavily substituted tetrahydrofuran, while the second, an approach to swazinecic acid, takes (*S*)-(-)-citronellal towards one of the most highly functionalized necic acids found in pyrrolizidine alkaloids.

CHAPTER II

ASYMMETRIC SYNTHESIS OF (+)-NEMORENSIC ACID

The successful exploitation of the relatively inexpensive monoterpene (*R*)-(+)-citronellal (**102**) as a starting material for synthesis of the necic acids of integerrimine[46-47,49] and usaramine[48-49] opens a broad approach to structurally diverse constituent acids of macrolactone pyrrolizidine alkaloids such as nemorensic acid and swazinecic acid. Previous studies in these laboratories supported the concept that the same monoterpene would be a valuable starting material for a synthesis of (+)-nemorensic acid (**25**)[46-49] since the latter contains a secondary methyl group where the correct configuration can be acquired from **102**. Moreover, **102** bears a functionalitic that can be easily amended for synthetic manipulation towards that of **25**.

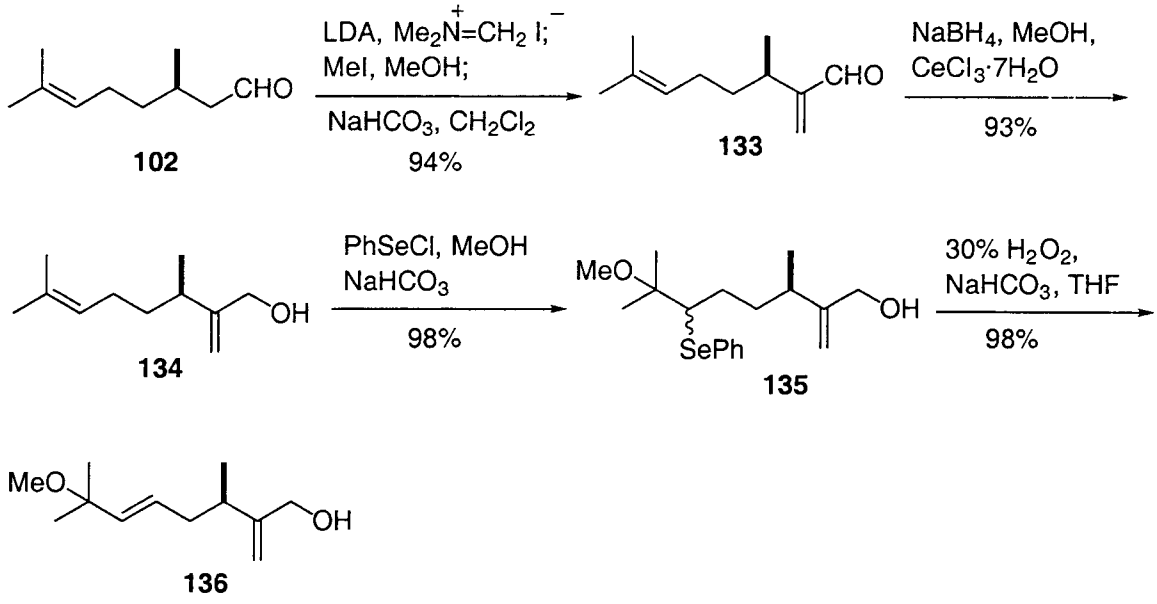
An intramolecular conjugate addition of an alkoxide to the α,β-unsaturated ester in **150** was envisioned as the key step in our asymmetric approach to (+)-nemorensic acid (**25**) (**Scheme 19**). The anion **150** would be generated from desilylation of **142**, which would be obtained by functional group manipulation of **137,** including a regioselective opening of the epoxy function. The alkene **137** would be derived from methoxyselenylation of **134** through a modification of the Toshimitsu reaction in which the trisubstituted olefin would undergo selective transposition in the presence of the disubstituted olefin. The allylic alcohol **134** was to be synthesized from commercially available (*R*)-(+)-citronellal (**102**) by α-methylenation in this retrosynthetic analysis.



Scheme 19

α-Methylenation[73] of **102** was accomplished by treatment of its lithium enolate with Eschenmoser's salt, followed by methylation of the intermediate dimethylamine and elimination with aqueous sodium bicarbonate. This protocol gave α,β-unsaturated aldehyde **133** in 94% overall yield. The aldehyde **133** was reduced under Luche conditions[74] with sodium borohydride in the presence of cerium(III) chloride heptahydrate to furnish **134** in 93% yield. The more electron-rich trisubstituted olefin in diene **134** was then selectively transposed in a two-step procedure. In the first step, methoxyselenation of **134** under modified Toshimitsu conditions[75] with phenylselenyl chloride and methyl alcohol as the nucleophile afforded **135**. This was oxidized with hydrogen peroxide and the resultant selenoxide

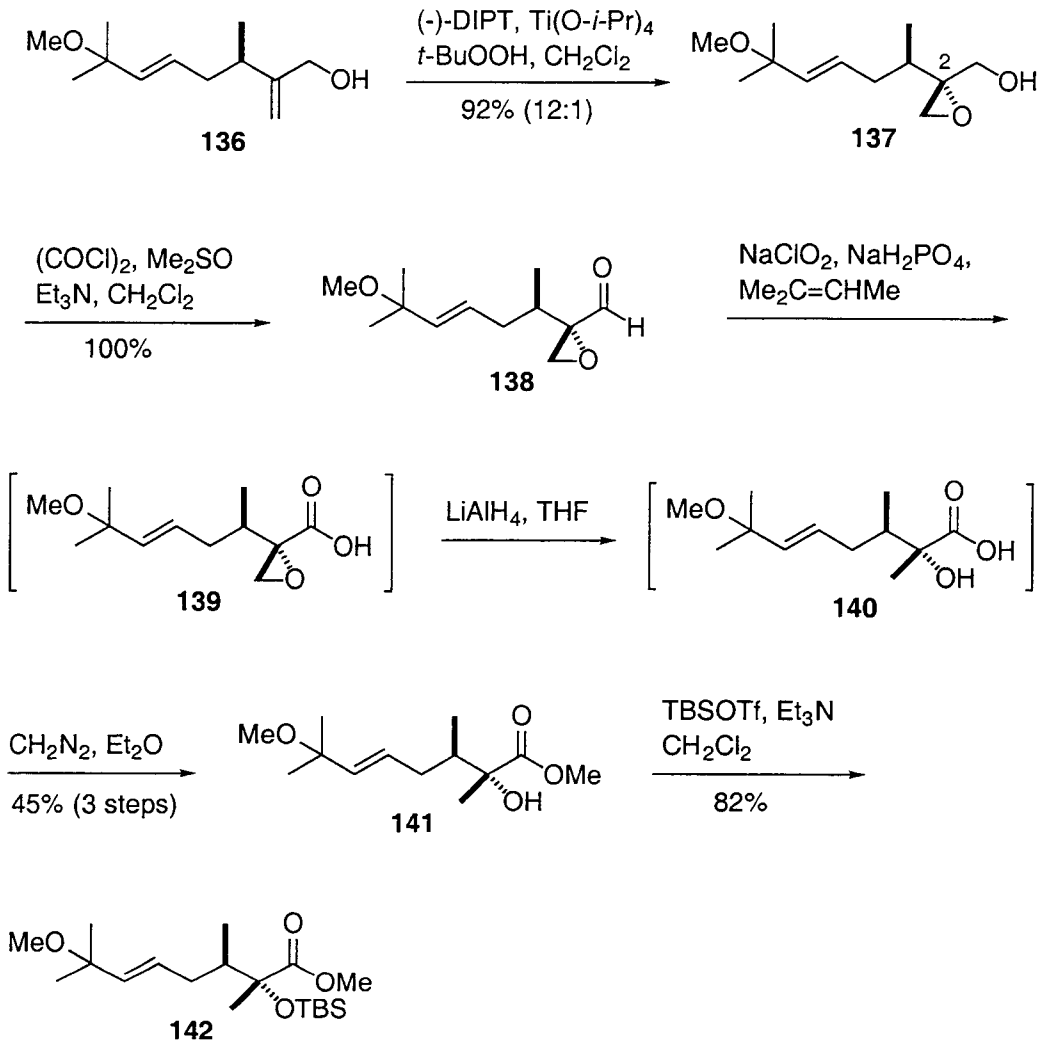
underwent in-situ elimination to give the allylic methyl ether **136** (**Scheme 20**).



Scheme 20

Sharpless epoxidation[76] of the allylic alcohol **136** with *tert*-butyl hydroperoxide using titanium tetraisopropoxide and (-)-diisopropyl tartrate (DIPT) as catalyst afforded the desired epoxide **137** accompanied by its C-2 epimer (12:1 ratio as determined by ^{13}C NMR spectroscopy). Epoxy alcohol **137** underwent Swern oxidation[77] to the corresponding aldehyde **138** in quantitative yield, and the aldehyde was further oxidized[78] to carboxylic acid **139**. The epoxy acid **139** without purification was treated with lithium aluminum hydride,[49,79] resulting in selective reduction of the epoxide moiety to yield the α-hydroxy acid **140**. The latter was immediately converted to its methyl ester **141** in an overall yield of 45% based on **137**. Finally, silylation[80]

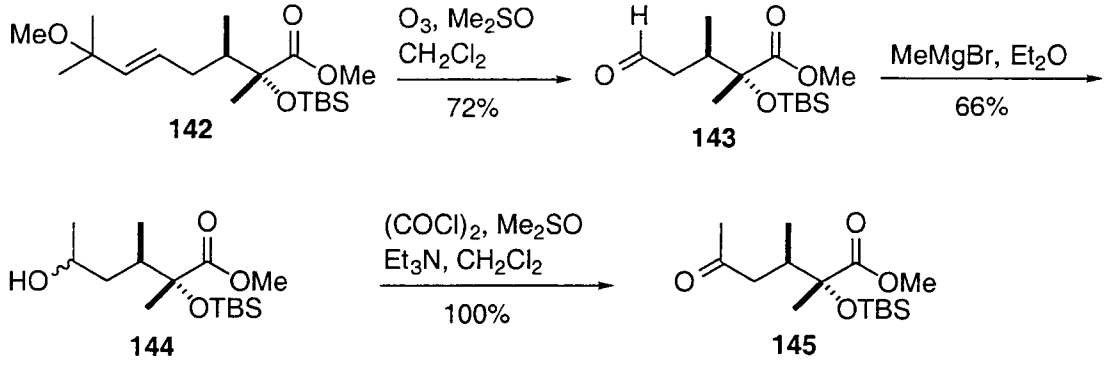
of the tertiary alcohol in **141** furnished the desired ether **142** in 82% yield (**Scheme 21**).



Scheme 21

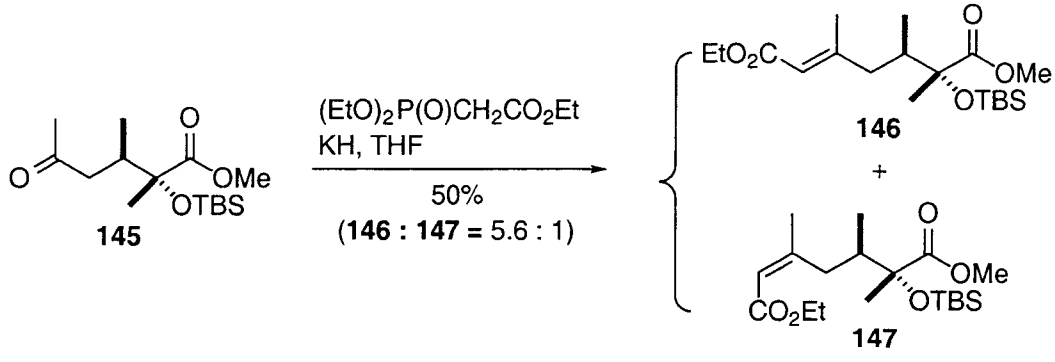
Cleavage of the alkene function of **142** and transformation to methyl ketone **145** was accomplished in three steps (**Scheme 22**). Thus, ozonolysis of **142**, followed by reduction of the intermediate ozonide with dimethyl sulfide,[81] afforded the aldehyde **143** in good yield. Sequential treatment of

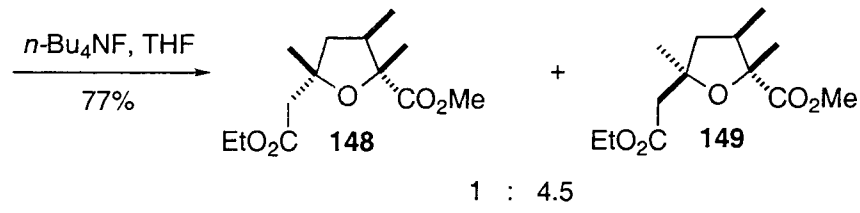
143 with methylmagnesium bromide provided alcohol **144** as a mixture of two diastereomers. Without separation, these alcohols were oxidized under Swern conditions[77] to give a single ketone **145** in quantitative yield.



Scheme 22

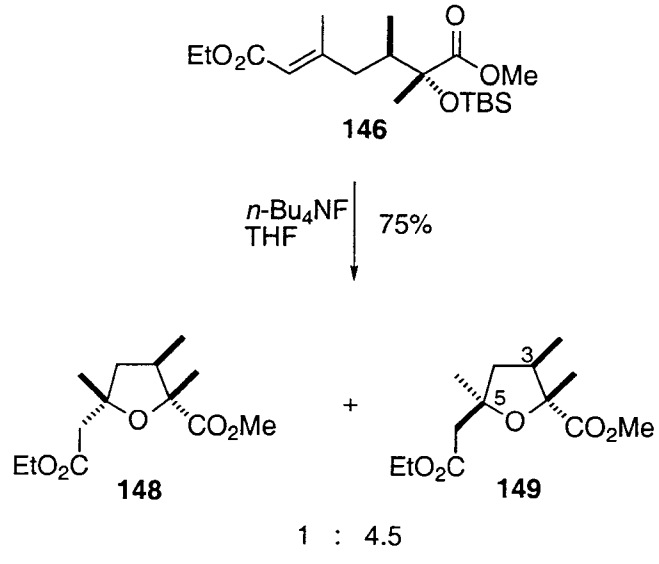
Wadsworth-Emmons olefination[82] of keto ester **145** with triethyl phosphonoacetate produced a 5.6:1 mixture of (*E*)- and (*Z*)-α,β-unsaturated esters, **146** and **147**. When a mixture of the two isomers was exposed to tetra-*n*-butylammonium fluoride (*n*-Bu4NF),[83] the derived alkoxy anion underwent spontaneous cyclization to a mixture of tetrahydrofurandicarboxylic esters **148** and **149** in a 1 : 4.5 ratio (**Scheme 23**).





Scheme 23

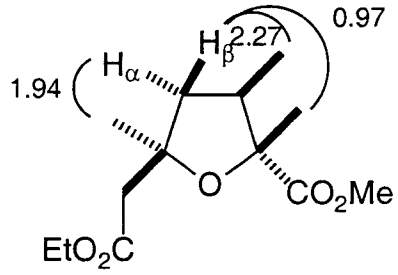
The same ratio (1:4.5) of **148** and **149** was obtained by deprotection of pure (*E*)-isomer **146** with tetra-*n*-butylammonium fluoride[83] followed by cyclization, thus proving that an equilibrium mixture of products had been reached (**Scheme 24**).



Scheme 24

Stereoisomers **148** and **149** were separated by HPLC (250 X 4.6 mm silica column, 15:1 hexane-ethyl acetate, 3 mL/min), and the major stereoisomer **149** was shown to possess 2,5-*trans* configuration at the

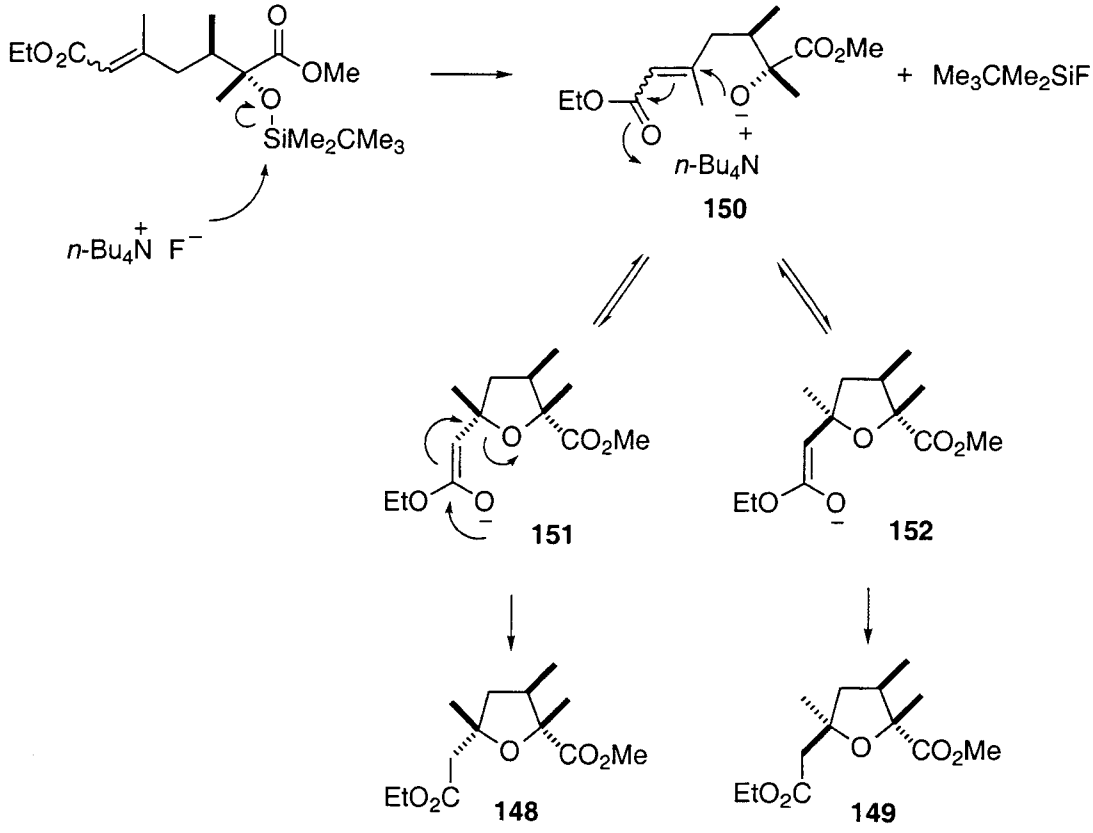
tetrahydrofuran by a nuclear Overhauser enhancement (nOe) experiment. In this NMR experiment, Hα at C-4 was correlated with methyl protons at C-5, and Hβ was correlated with methyl signals at C-2 and C-3 (**Figure 2.1**).



149

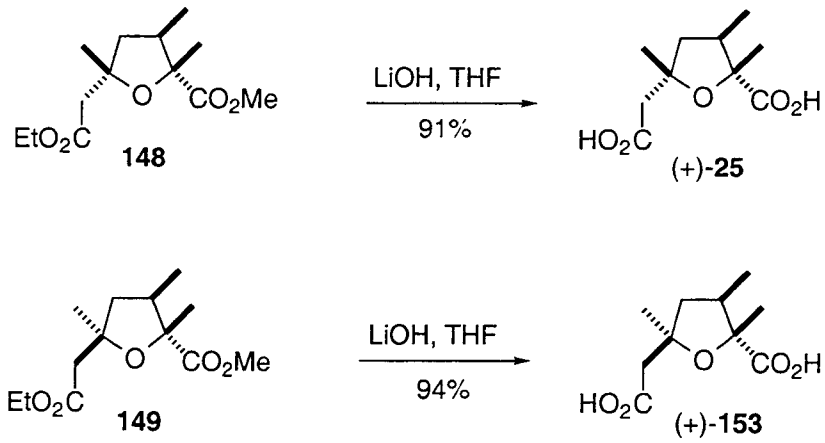
Figure 2.1. Nuclear Overhauser Enhancement (nOe) Diagram of **149**.

The tetrahydrofuran **149** was presumed from the foregoing results to be the thermodynamically more stable product of cyclization of **146** and **147** (**Scheme 25**). When either the (*E*)- or (*Z*)-olefin is treated with tetra-*n*-butylammonium fluoride, the resulting alkoxy anion **150** can in principle attack the conjugated double bond from either face to give both cyclic intermediates **151** and **152**. However, under the reaction conditions, **151** and **152** must revert to alkoxy anion **150** in an equilibrium process, so that the major product from cyclization is the more stable tetrahydrofuran, i.e. **149**.



Scheme 25

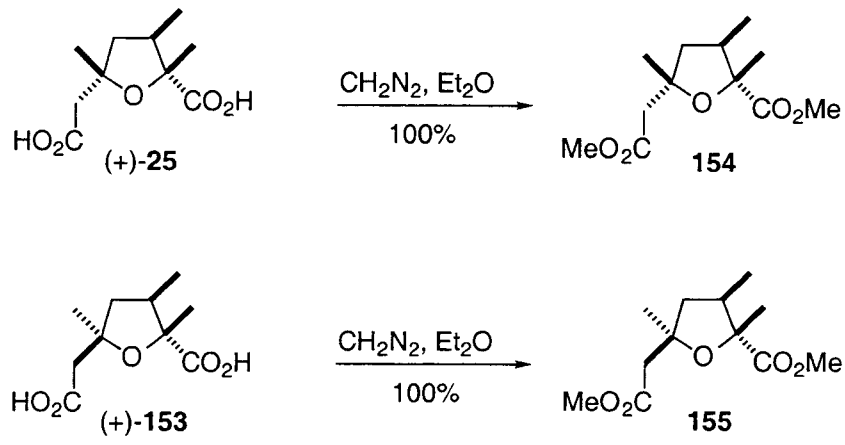
The properties of synthetic (+)-**25** obtained by saponification of **148**, were in excellent agreement with those reported[1] for the necic acid of (+)-nemorensine, thus proving that nemorensic acid has 2*R*,3*R*,5*S* configuration. On the other hand, saponification of **149** afforded (+)-**153** (5-*epi*-nemorensic acid) which exhibited spectroscopic properties clearly different from those recorded[1] for the hydrolysis product of (+)-nemorensine (**Scheme 26**).



148 (+)-25 149 (+)-153

Scheme 26

Conversion of synthetic (+)-**25** and (+)-**153** to their respective dimethyl esters, **154** and **155**, permitted further comparison with the naturally derived diester and again demonstrated that nemorensic acid has the absolute configuration represented by (+)-**25** (**Scheme 27**).



(+)-25 154 (+)-153 155

Scheme 27

Finally, the structure of natural nemorensic acid was confirmed by a single crystal X-ray analysis of its parent alkaloid nemorensine (**Figure 2.2**)

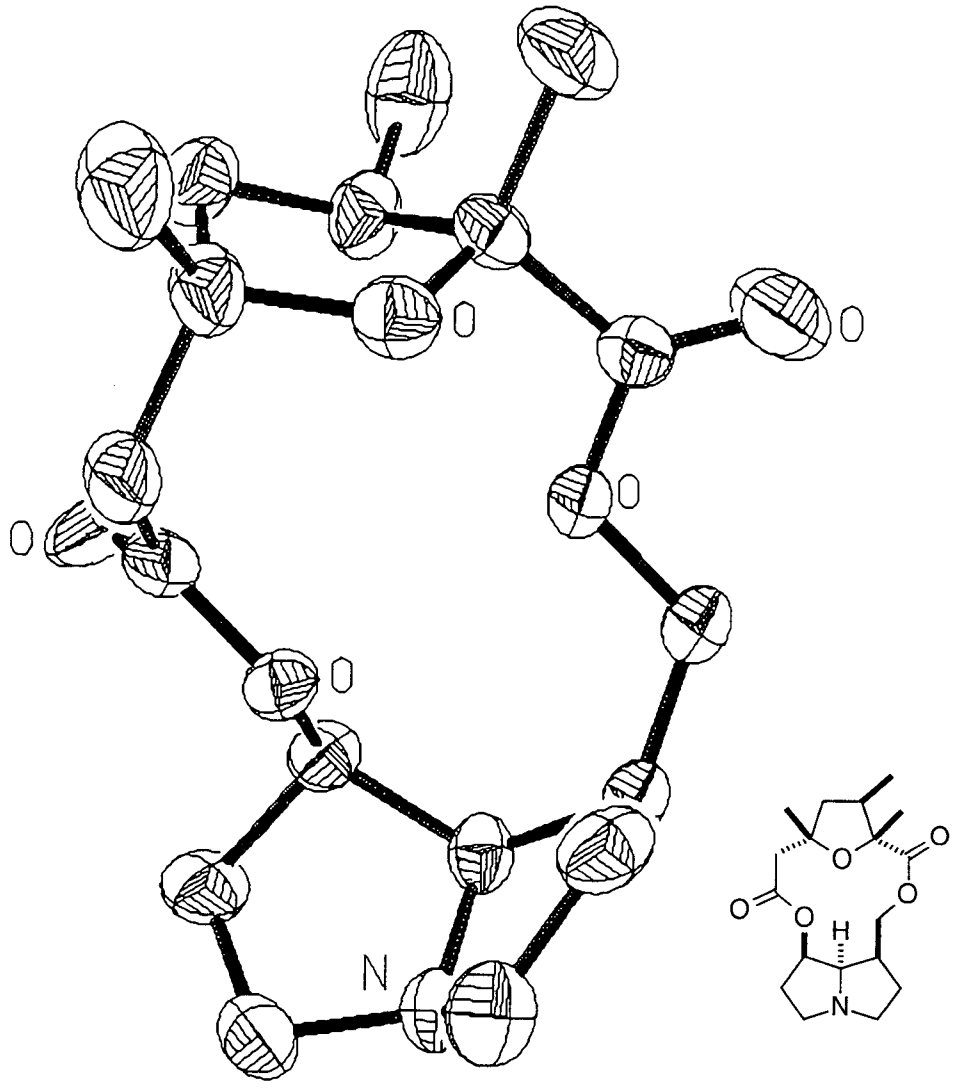
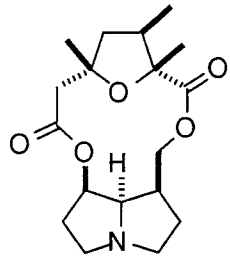
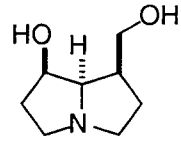


Figure 2.2. ORTEP Diagram from X-ray Crystallographic Analysis of (+)-Nemorensine (**1**).

This determination conclusively established the structure of nemorensine as **1**, in which the necic acid portion is shown to possess (2*R*,3*R*,5*S*) absolute configuration by virtue of its stereochemical relationship to the pyrrolizidine segment (-)-platynecine present as the necine base in the alkaloid. The absolute configuration of (-)-platynecine (**156**) has previously been assigned on the basis of chemical studies[84] as well as an enantioselective synthesis of this pyrrolizidine (**156**).[85]



(+)-Nemorensine (**1**)



(-)-Platynecine (**156**)

A comparison of the spectral properties of (+)-**25** and (+)-**153** with those reported for the necic acid derived from retroisosenine (**18**) indicates that neither of these substances corresponds to the necic acid of that alkaloid (**18**).[60] Whether retroisosenine is a yet unidentified stereochemical variant based on **18** remains to be determined.

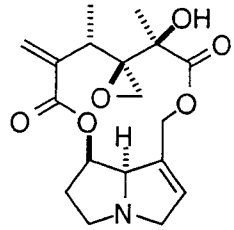
In conclusion, the first asymmetric synthesis of (+)-nemorensic acid (**25**) which was accomplished during this research proved that the original stereochemical assignments made to nemorensine as **17** or **23** and to retroisosenine as **18** were incorrect. The necic acid constituent of the pyrrolizidine alkaloid (+)-nemorensine is now shown to possess the stereochemistry of (+)-**25**. Furthermore, X-ray crystallographic analysis of

nemorensine together with this synthetic work has established that the complete stereostructure of the natural alkaloid is correctly represented by **1**.

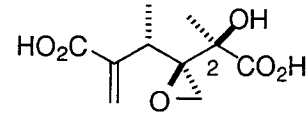
CHAPTER III

ASYMMETRIC SYNTHESIS OF 2-*epi*-SWAZINECIC ACID AND AN APPROACH TOWARDS THE ASYMMETRIC SYNTHESIS OF SWAZINECIC ACID

Swazinecic acid (**50**), the constituent acid of the dilactone pyrrolizidine alkaloid swazine (**2**), presents a demanding test of the general strategy developed in these laboratories for the synthesis of necic acids, from a readily available monoterpene in the chiral pool. Our approach, which employs (*S*)-citronellal as the starting material, hinges upon oxidative truncation of an elaborated monoterpenoid system to generate a dicarboxylic acid having the requisite functionality and configuration of the necic acid. The absolute configuration assigned to (-)-swazine (**2**) dictates that our point of departure towards **50** should be (*S*)-(-)-citronellal (**157**), the enantiomer of the starting material used for synthesis of nemorensic acid. Since our planned route to **50** involved early introduction of a relatively sensitive epoxide, it was essential that later steps in the sequence avoid reagents which could destroy this function.

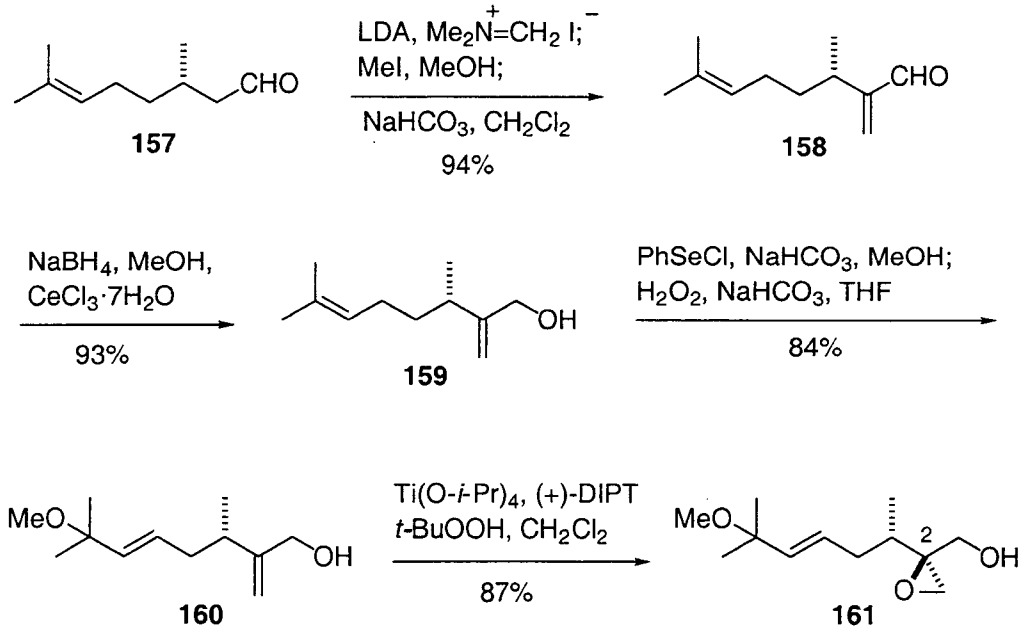


(-)-Swazine (**2**)



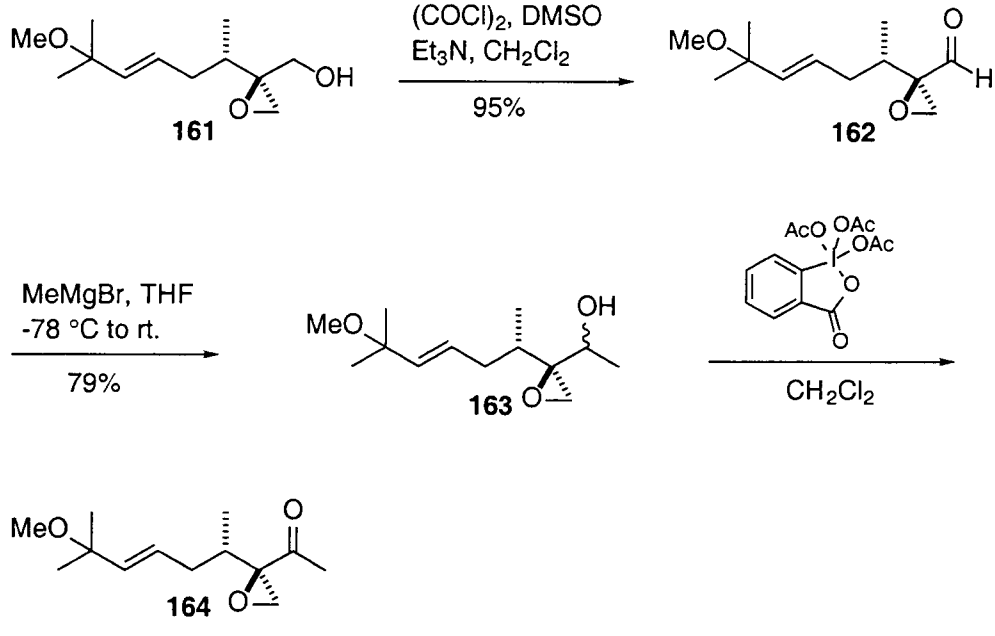
Swazinecic acid (**50**)

Following the procedure employed in the enantiomeric series for asymmetric synthesis of (+)-nemorensic acid (**25**),[67] α-methylenation[73] of (*S*)-(-)-citronellal (**157**) gave α,β-unsaturated aldehyde **158**. This was submitted to a Luche reduction[74] with sodium borohydride and cerium trichloride to afford the allylic alcohol **159**. The more electron-rich trisubstituted olefin in diene **159** underwent selective methoxyselenylation using a modification of Toshimitsu's conditions,[75] and after oxidation of the intermediate alkylselenide with hydrogen peroxide and in situ elimination of the selenoxide diene **160** was obtained. Sharpless epoxidation[76] of allylic alcohol **160** using (*S,S*)-(+)-diisopropyl tartrate (DIPT) gave the desired epoxy alcohol **161** as the major stereoisomer accompanied by the C-2 *epi* epoxide. The ratio of these stereoisomers was 13:1 as measured by ^{13}C NMR spectroscopy (**Scheme 28**).



Scheme 28

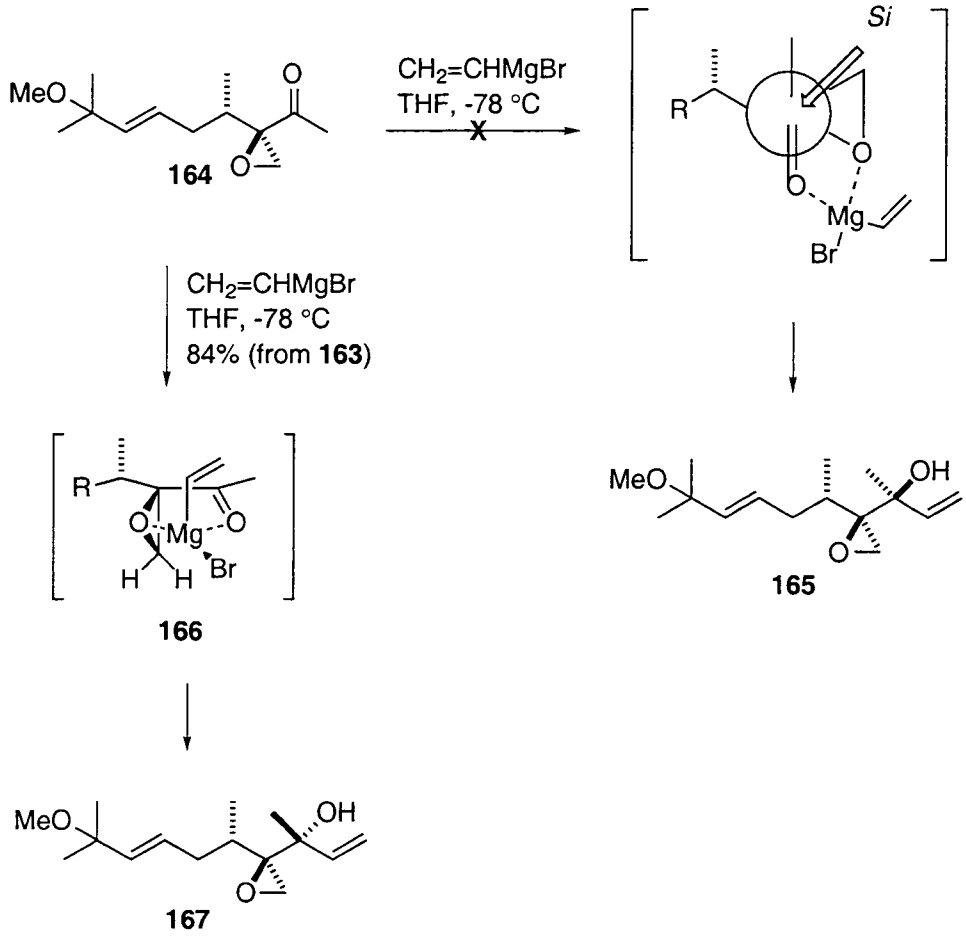
The primary alcohol **161** was oxidized to aldehyde **162** under Swern conditions,[77] and **162** was reacted with methylmagnesium bromide at low temperature to afford alcohol **163** as a mixture of two diastereomers. The mixture was converted to ketone **164** as a single isomer upon oxidation with Dess-Martin periodinane[86] (**Scheme 29**).



Scheme 29

It was presumed that chelation-controlled Grignard addition to ketone **164** would be directed by the epoxide and would therefore occur selectively at the *si* face of the carbonyl group to give (*S*) alcohol **165**. In fact, when **164** was treated carefully with vinylmagnesium bromide at low temperature, a single alcohol was obtained in high yield (**Scheme 30**). However the configuration of the tertiary alcohol in this product was subsequently found to be (*R*), the result of *re* face attack of Grignard reagent on ketone **164**. It is believed that chelation

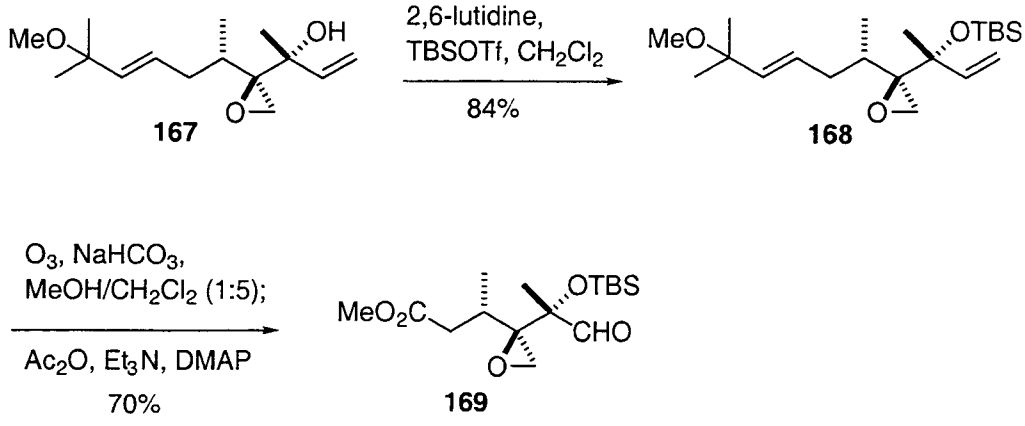
between the epoxide oxygen, ketone and vinylmagnesium bromide occurs as shown in **166**, so that intramolecular delivery of the vinyl group to the carbonyl carbon takes place preferentially from the *re* face rather than the *si* face as had been expected. The configuration of the tertiary alcohol in **167** was conclusively proved by X-ray crystallographic analysis of a later compound in this sequence.



Scheme 30

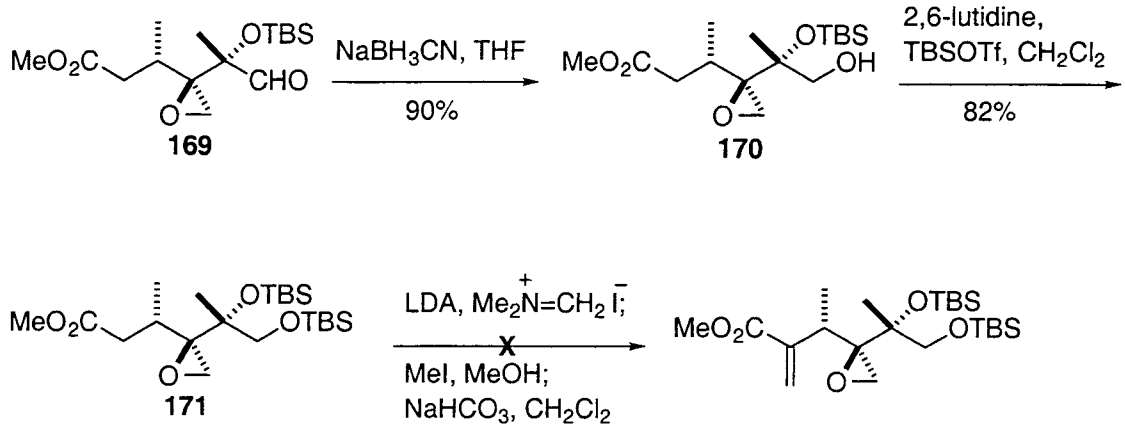
The tertiary alcohol **167** was protected as its *tert*-butyldimethylsilyl ether **168**,[80] and an attempt was then made to cleave both olefins simultaneously to

yield a dicarboxylic acid. Conventional ozonolysis, using an oxidative work-up, failed to produce a useful product from **168**. On the other hand, ozonolytic cleavage of **168** as described by Schreiber[87] gave the aldehyde ester **169** in excellent yield (**Scheme 31**). This convenient protocol not only differentiated the termini of **169** by oxidation level, but did so in a highly selective manner.



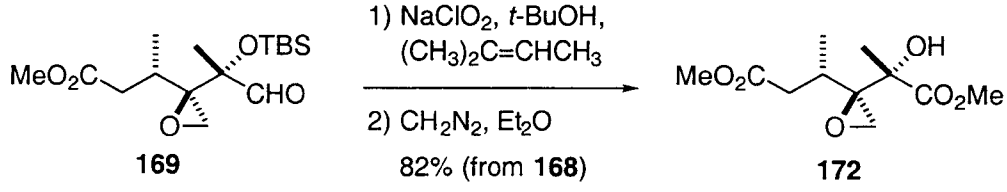
Scheme 31

Unfortunately, the inherent instability of **169** resulting from its propensity for intramolecular aldol condensation demanded immediate reduction of this aldehyde to its corresponding alcohol or oxidation to a carboxylic acid. Selective reduction of the aldehyde in **169** with sodium cyanoborohydride[88] was accomplished in high yield, and the resulting primary alcohol **170** was protected as its *tert*-butyldimethylsilyl (TBS) ether **171**[80] (**Scheme 32**). However, attempted α-methylenation of ester **171** with Eschenmoser's salt was unsuccessful, and only the starting material **171** was recovered.



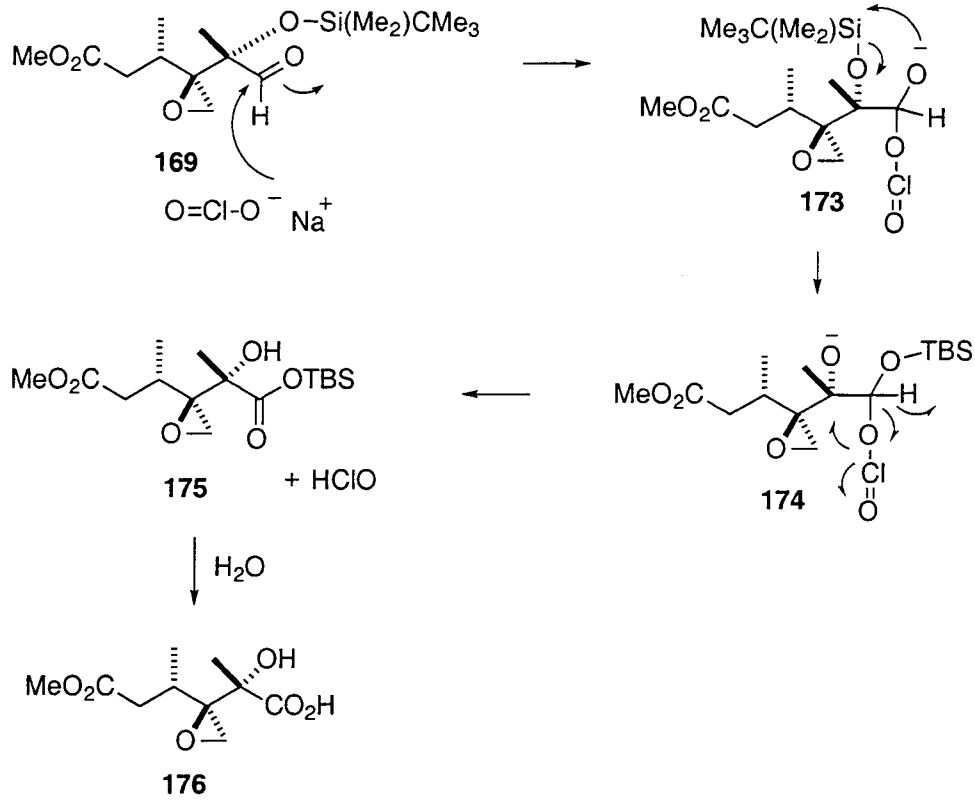
Scheme 32

In an alternative route from **169** the aldehyde was oxidized to a carboxylic acid[78] which was then treated with diazomethane to produce dimethyl ester **172** (**Scheme 33**).



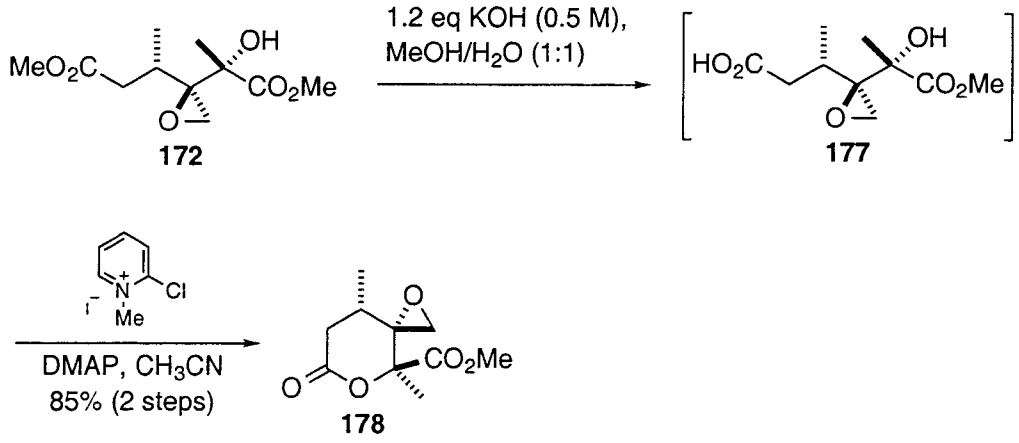
Scheme 33

Unexpectedly, the silyl ether of **169** was cleaved in the course of its oxidation to carboxylic acid with sodium chlorite. It is likely that nucleophilic addition of chlorite ion to the carbonyl carbon in **169** produced an α-alkoxy anion **173**, which then underwent a 1,2-silyl shift to give **174**. The oxygen-chlorine bond would be broken in a radical process to give the silyl ester **175**, which would be hydrolyzed to α-hydroxy acid **176** (**Scheme 34**).



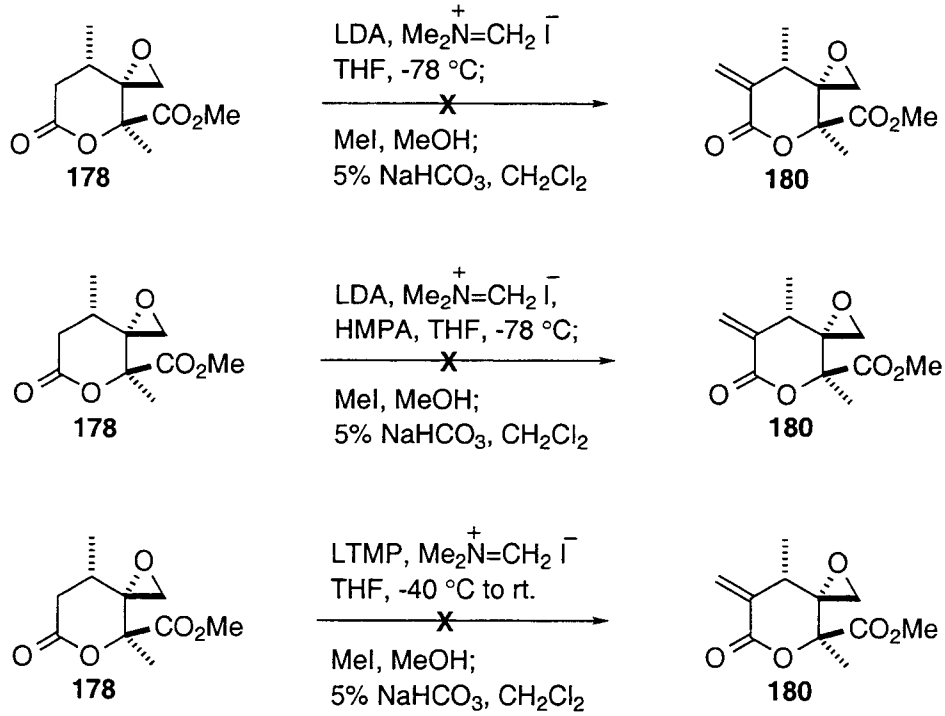
Scheme 34

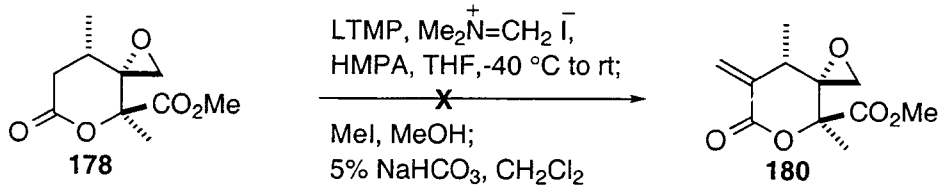
Although the protecting group was easily replaced in **172**, attempts to introduce an α-methylene function into this acyclic diester were again foiled by an intramolecular reaction of the ester enolate, in this case a facile Dieckmann condensation to a cyclopentenone. Reasoning that an *exo* methylene group might be more easily incorporated into a δ-lactone derived from **172**, the latter was subjected to careful saponification with the result that the more exposed ester was cleaved with very high selectivity. The resultant δ-hydroxy acid **177** was easily converted to lactone **178** using Mukaiyama's reagent[89] (**Scheme 35**).



Scheme 35

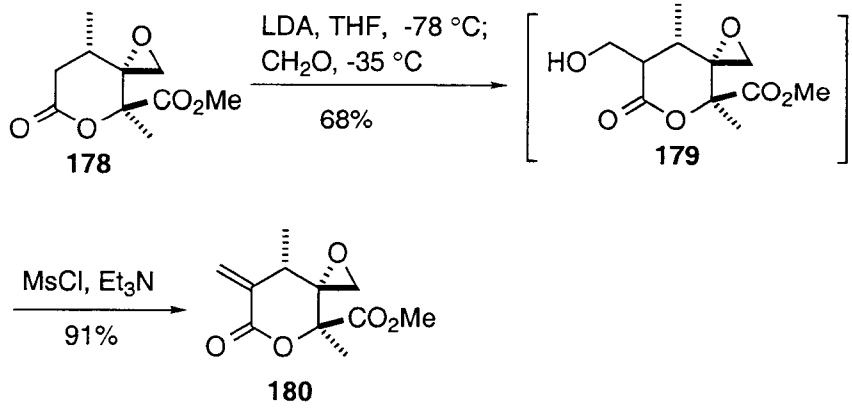
To our disappointment, all attempts to effect α-methylenation of **178** with Eschenmoser's salt under a variety of conditions[73,90] were unsuccessful (**Scheme 36**). In most cases, only starting material was recovered.





Scheme 36

It is known that certain ketones such as cyclohexanone are rather unreactive toward Eschenmoser's reagent under conventional conditions.[73] The same situation obtains with **178**, and therefore a more reactive reagent than Eschenmoser's salt is clearly required in order to introduce the *exo* methylene group into the δ-lactone. In fact, formaldehyde is just such a reagent, and it was found that treatment of **178** with base and then with gaseous formaldehyde afforded the unstable β-hydroxy lactone **179** in good yield. Exposure of **179** to methanesulfonyl chloride led directly to *exo* methylene δ-lactone **180** in excellent yield (**Scheme 37**).[91]



Scheme 37

Lactone **180** crystallized from diethyl ether-chloroform as well formed needles which proved to be suitable for X-ray crystallographic analysis (**Figure 3.1**). The X-ray crystal structure fully confirmed the relative configuration of this lactone and thus proved that the tertiary alcohol resulting from vinylmagnesium bromide addition to ketone **164** has the stereochemistry shown in **167**.

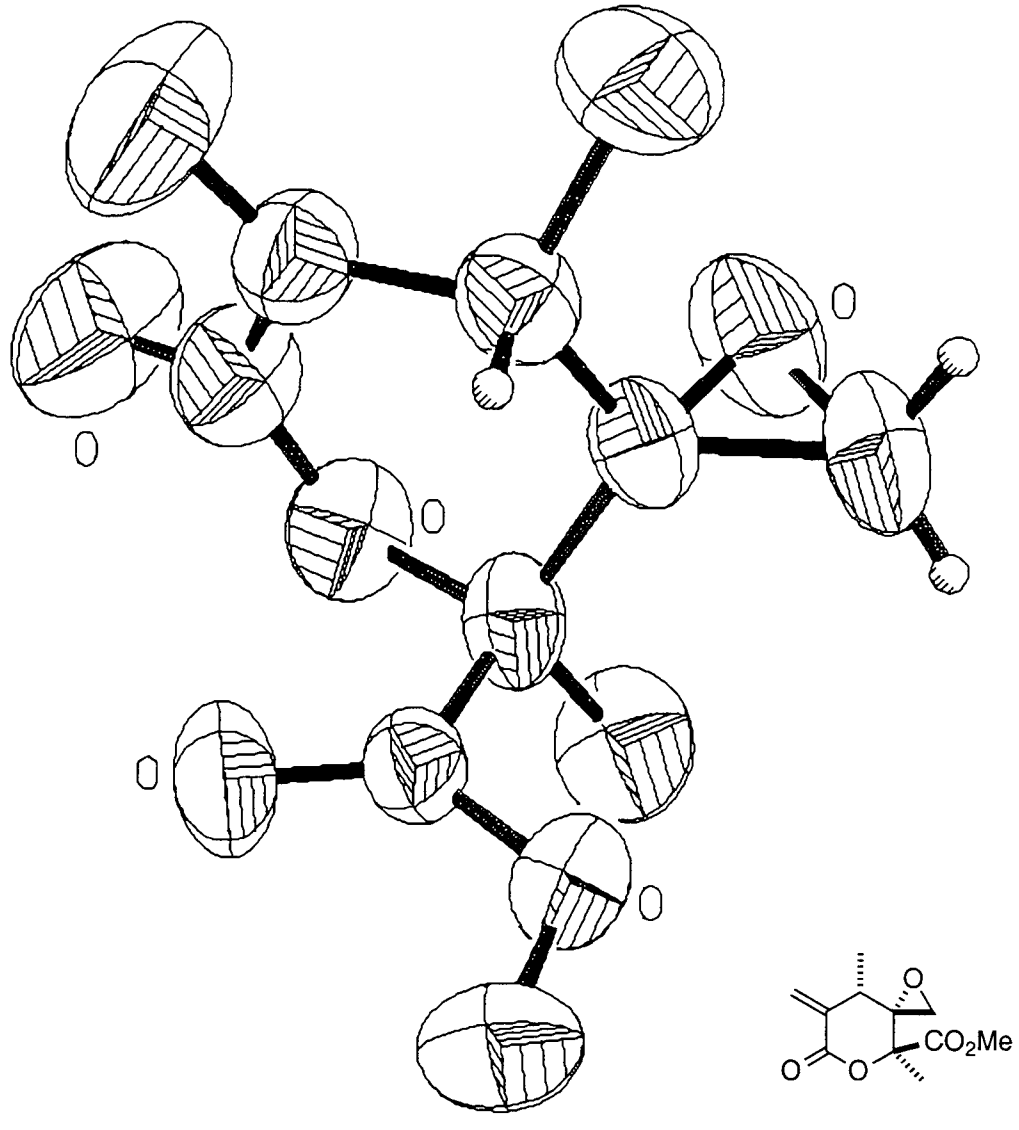
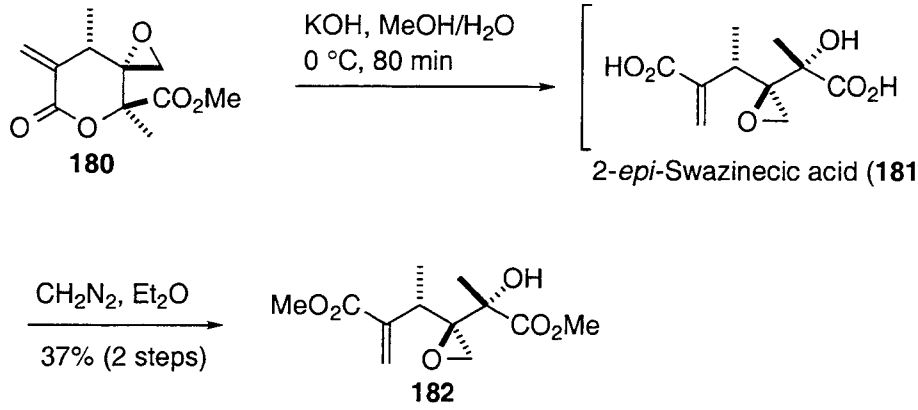


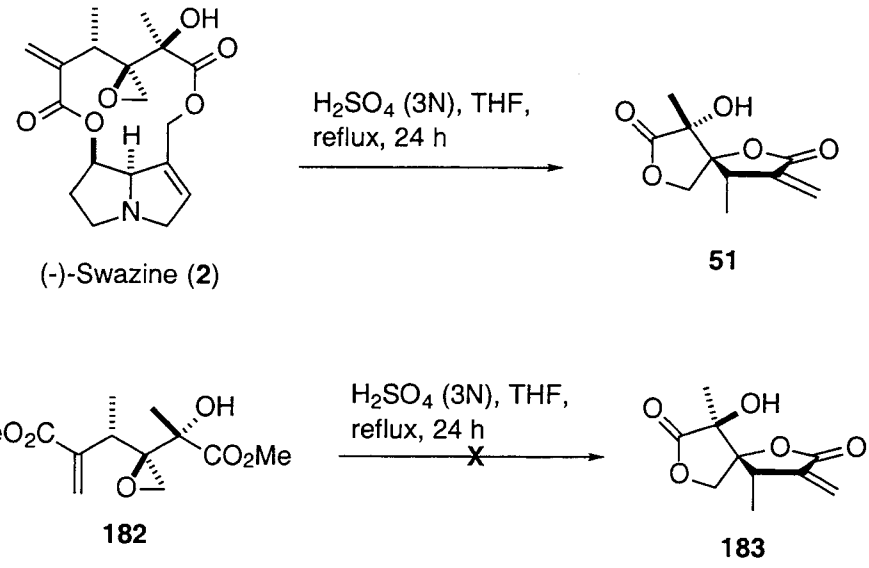
Figure 3.1. ORTEP Diagram from X-ray Crystallographic Analysis of **180**.

Basic hydrolysis of **180** gave the unstable 2-*epi*-swazinecic acid (**181**) which was isolated and characterized as its dimethyl ester (-)-**182** after exposure to diazomethane (**Scheme 38**).



Scheme 38

It is known from X-ray crystallographic analysis of its *p*-bromobenzoate that the spirodilactone **51** derived from natural (-)-swazine (**2**) upon treatment with hot sulfuric acid has the *S* configuration at the spiro center. This implies retention of configuration in the opening of the epoxide.[2] It was assumed that when dimethyl ester **182** was treated under the same reaction conditions as **2**, spirodilactone **183** with the same *S* configuration at the spiro center as **51** would result (**Scheme 39**).



(-)-Swazine (**2**)

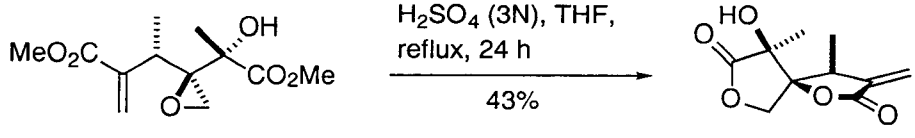
51

182

183

Scheme 39

Surprisingly, when **182** was exposed to refluxing sulfuric acid, the epoxide was opened with inversion of configuration, producing the crystalline spirodilactone **184** with *R* configuration at the spiro center (**Scheme 40**). The stereochemistry of **184** was fully confirmed by an X-ray crystallographic analysis (**Figure 3.2**).



182

184

Scheme 40

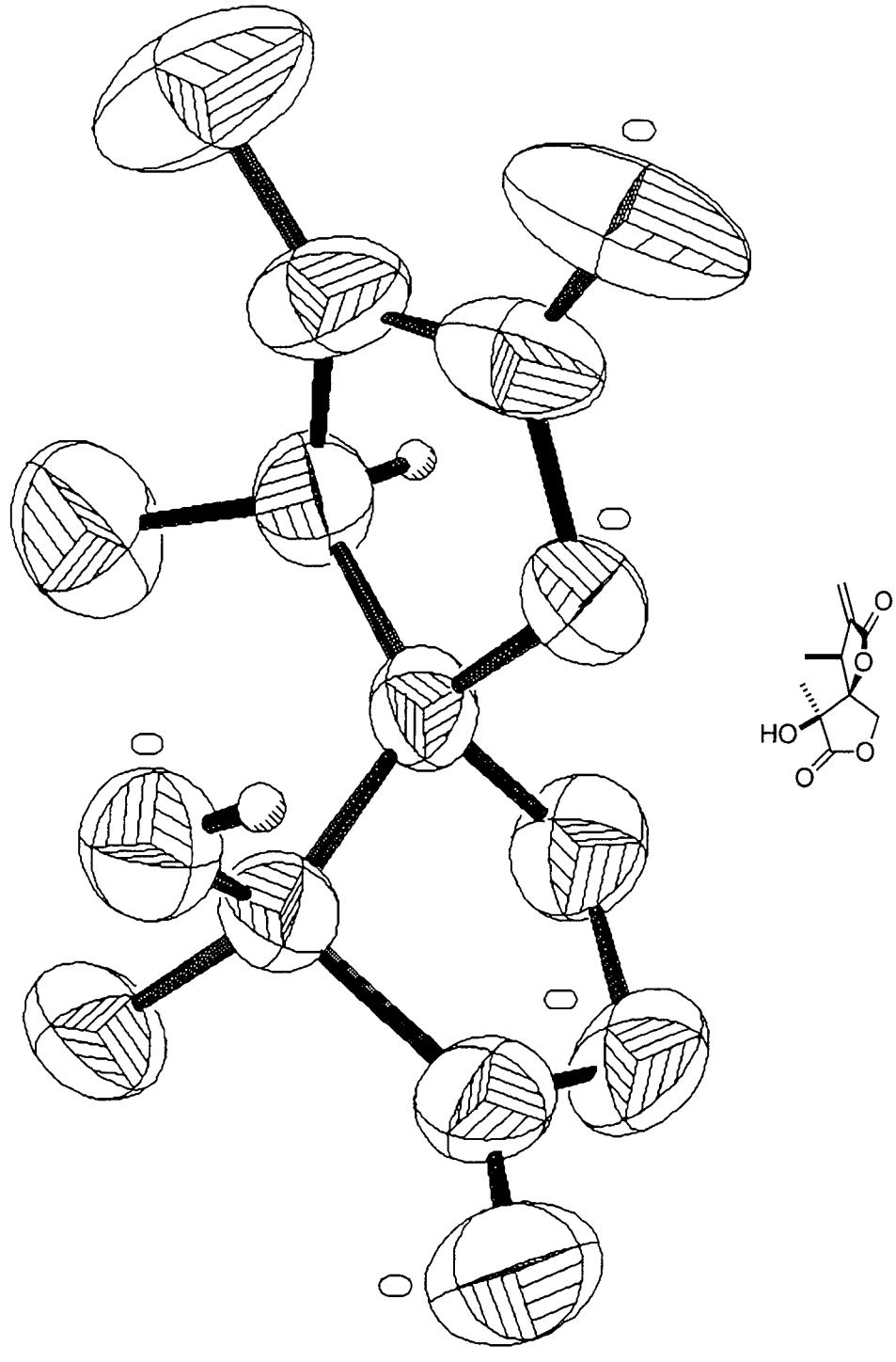
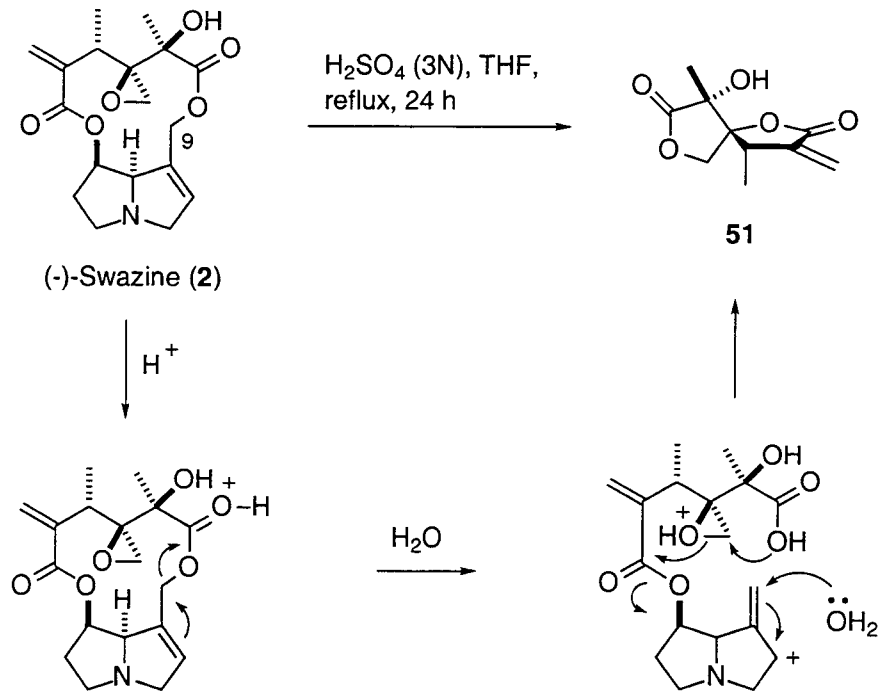


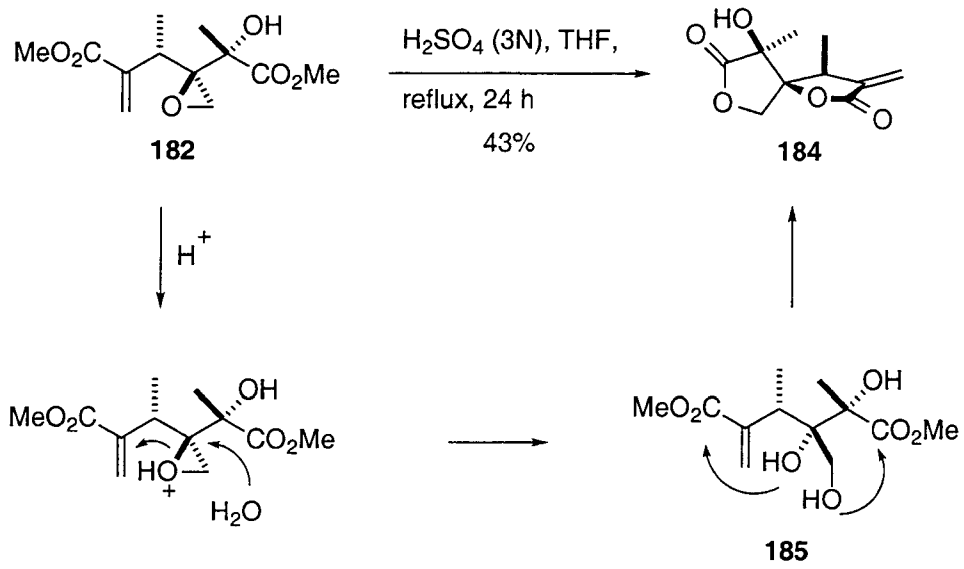
Figure 3.2. ORTEP Diagram from X-ray Crystallographic Analysis of **184**.

An explanation for the divergent behavior of swazinecic acid derived from acidic hydrolysis of the parent alkaloid and 2-*epi*-swazinecic acid derived from **182** probably lies in the nature of the ester groups. First, it is clear that the two spirodilactones **51** and **184** are the result of different reaction pathways rather than some fortuitous event which scrambles the epoxide configuration in route to the spirodilactones. It is known that the primary ester linkage (at C-9) of pyrrolizidine alkaloids is normally the most susceptible to hydrolysis, especially if it is an allylic ester as in unsaturated pyrrolizidine alkaloids such as swazine.[3,6] In the case of swazine (**2**), the liberated carboxylic acid is able to attack the protonated epoxide at the less substituted terminus with consequent retention of configuration at the tertiary center and formation of a five-membered lactone. The liberated tertiary alcohol then reacts with the remaining ester carbonyl function to form spirodilactone **51** (**Scheme 41**).



Scheme 41

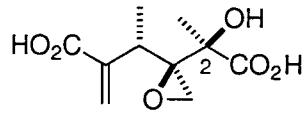
The ester functions of **182**, on the other hand, are more resistant to acidic hydrolysis and a different reaction pathway to the spirodilactone intervenes. If the epoxide is first protonated, Markownikoff addition by water to the epoxide results in inversion of the tertiary center and leads to diol intermediate **185**.[92] The spirodilactone **184** would then be formed by a double cyclization of the diol diesters (**Scheme 42**).



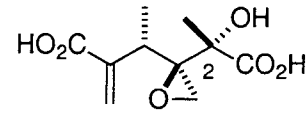
Scheme 42

The configuration of the tertiary alcohol in **181** is epimeric with that of swazinecic acid (**50**). In principle, a straightforward modification of the route to **181** could reverse the configuration at C-2 and thus could lead to a synthesis of swazinecic acid (**50**). The tertiary C-2 stereocenter of **181** was generated in the chelation-controlled addition of vinylmagnesium bromide to methyl ketone (**164**), and it seemed plausible that the configuration of this stereocenter could

be inverted by simply reversing the sequence of methyl and vinyl Grignard additions.

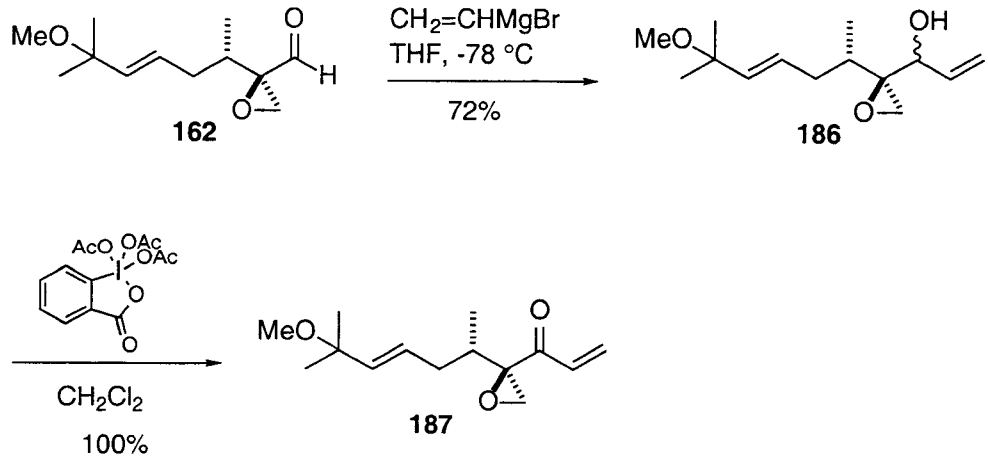


Swazinecic acid (**50**)



2-*epi*-Swazinecic acid (**181**)

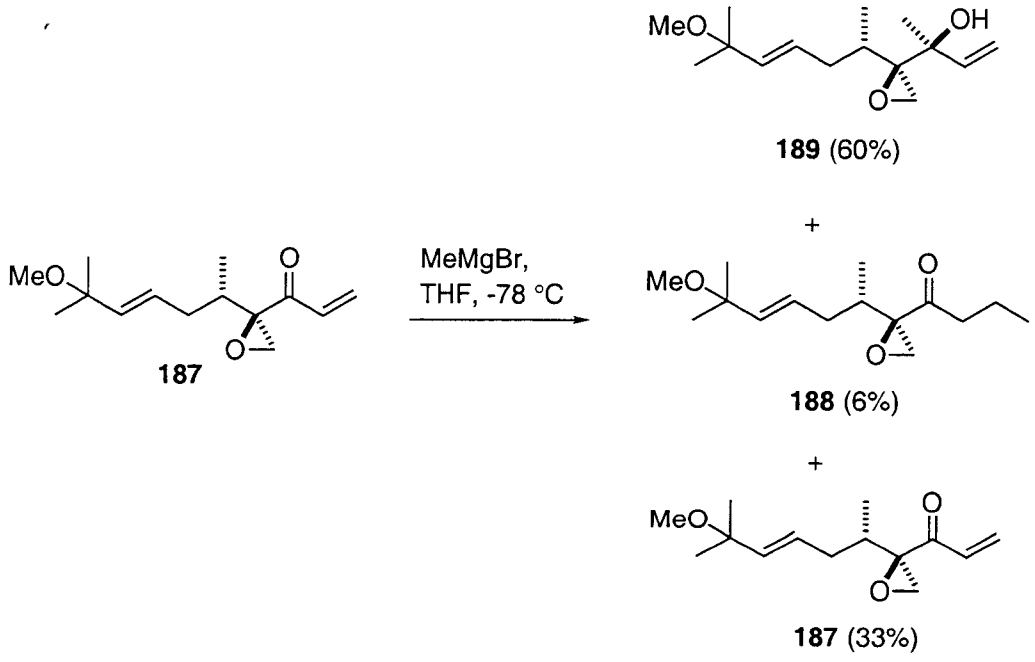
The revised route towards swazinecic acid now required an initial Grignard reaction of aldehyde **162** with vinylmagnesium bromide. This gave allylic alcohol **186**, which was oxidized to α,β-unsaturated ketone **187** with Dess-Martin periodinane (**Scheme 43**).[86]



Scheme 43

The second Grignard reaction, a chelation-controlled addition of methylmagnesium bromide to the ketone **187** was expected to occur selectively

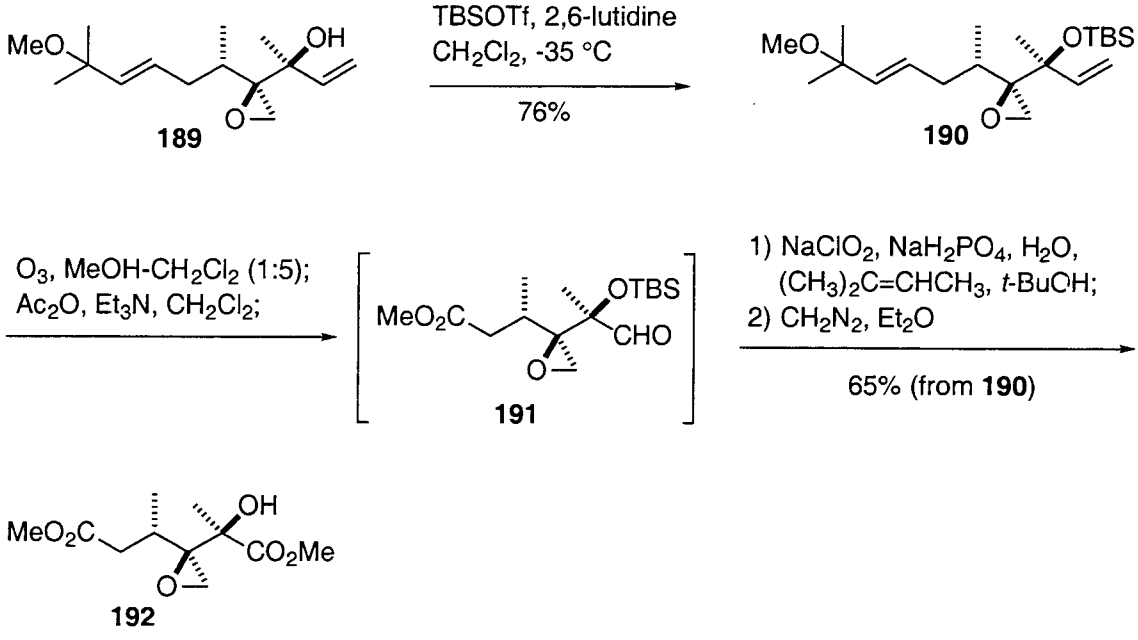
at the *re* face of the carbonyl group as a result of the directing effect of the epoxide previously seen with Grignard addition to **164**. However, this reaction was complicated by competition between 1,2- and 1,4-addition of methylmagnesium bromide to **187**. It was found that this problem could be overcome by slow addition of a dilute solution of the Grignard reagent to **187** at low temperature, a protocol which led to the desired kinetically-controlled 1,2-adduct **189** as the major product. The minor quantity of 1,4-addition product (**188**) formed in this reaction could be easily removed by flash chromatography (**Scheme 44**).



Scheme 44

The alcohol **189** was converted to dimethyl ester **192** by the same reaction sequence used with **167**. Thus, **189** was first protected as its *tert*-butyldimethylsilyl ether **190** which was subjected to ozonolytic cleavage as

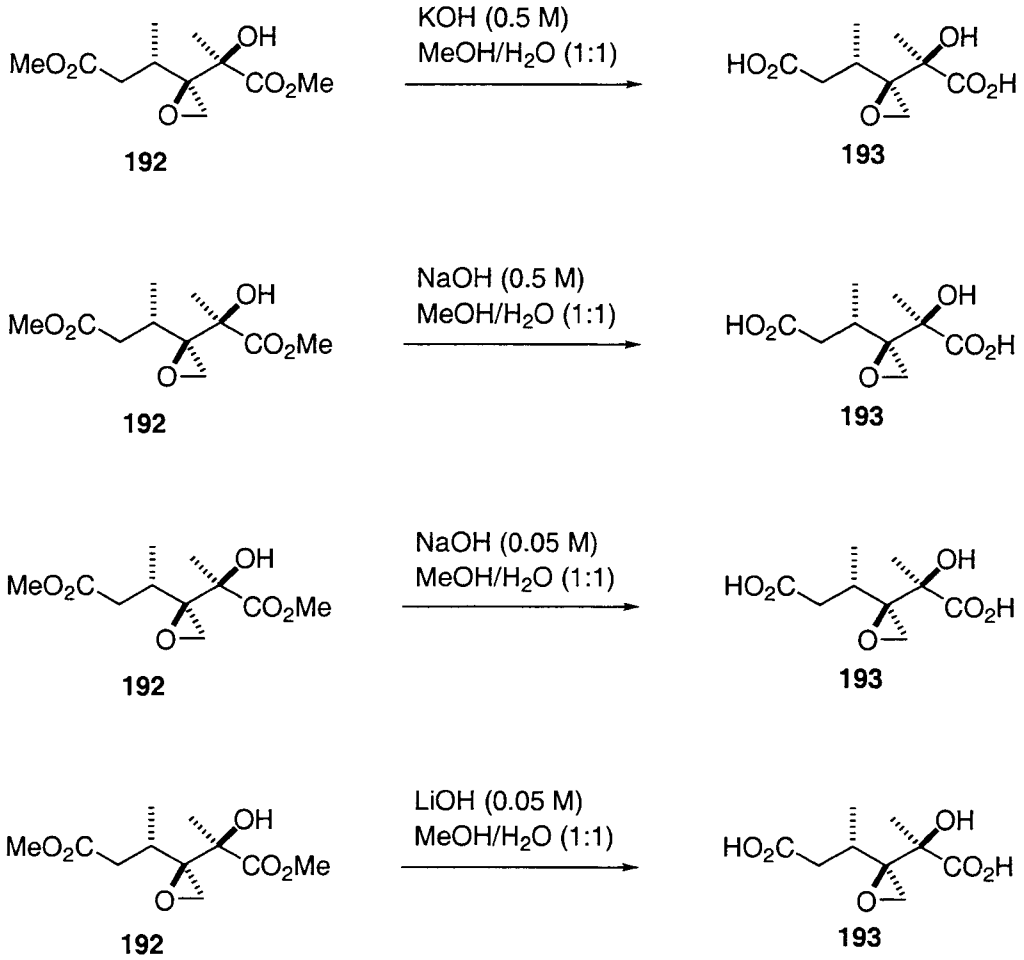
described by Schreiber.[87] This gave the expected aldehyde ester **191**, which was oxidized directly to the corresponding carboxylic acid. As before, the silyl ether was cleaved from **191** in the course of its oxidation with sodium chlorite. The resulting α-hydroxy carboxylic acid was immediately esterified with diazomethane to afford dimethyl ester **192** (**Scheme 45**).



Scheme 45

It was expected that selective hydrolysis of the more exposed ester function of **192** could be accomplished by the same protocol used for selective saponification of its C-2 epimer **172**. However, all attempts at monohydrolysis of **192** resulted in immediate cleavage of both methyl esters (**Scheme 46**). Apparently, the steric hindrance due to the adjacent tertiary center in **172** which prevents saponification of the α-hydroxy ester is absent in the (*R*) stereoisomer

192, resulting in relatively little difference in reactivity between the two ester groups towards basic reagents.

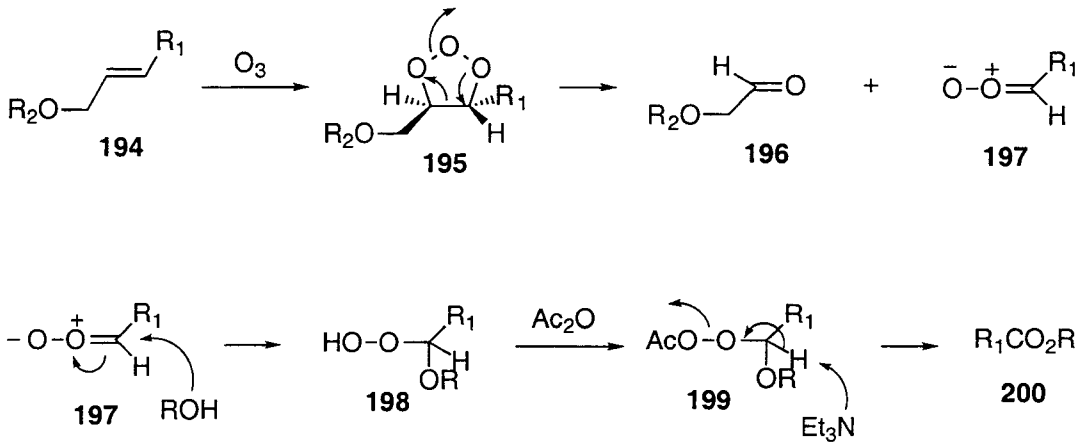


Scheme 46

The failure to effect selective hydrolysis of dimethyl ester **192** required that differentiation of the ester termini be accomplished by some other means. Since a benzyl ester can be cleaved by hydrogenolysis under conditions which leave a methyl ester intact, a solution to this problem was available in principle through a mixed diester such as **202**. The accepted mechanism of ozonolysis

as carried out under Schreiber's conditions suggests that if benzyl alcohol is present during the reaction with **190**, it should produce a benzyl ester at the more exposed cleavage site.

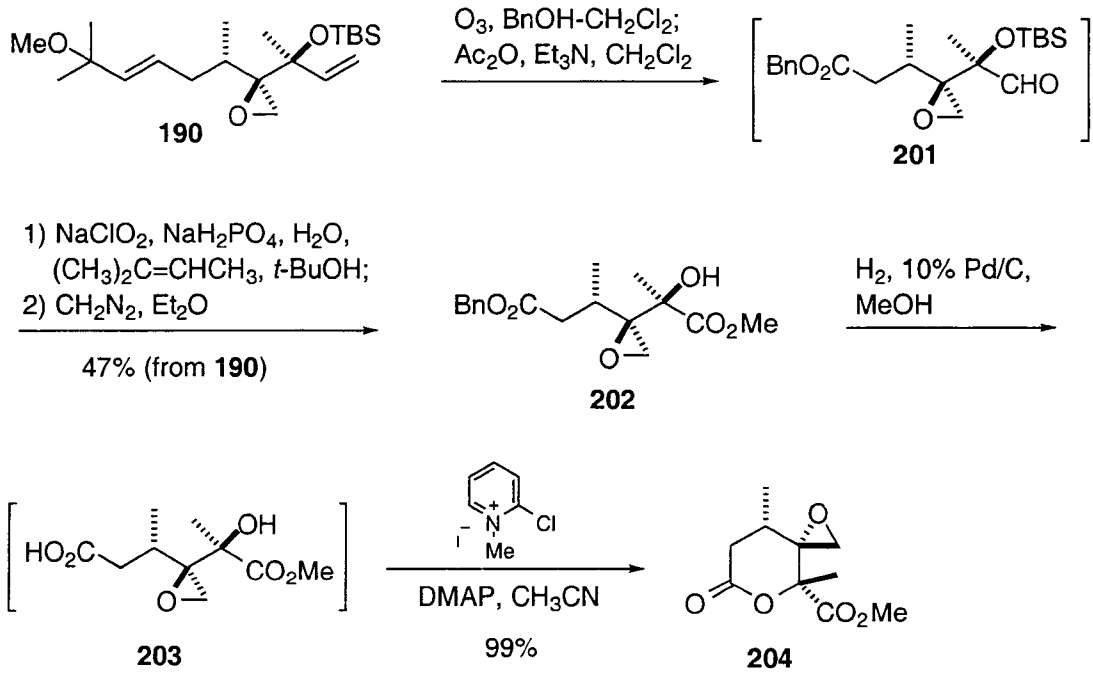
The mechanism of ozonolysis of an unsymmetrical alkene is shown in **Scheme 47**. Ozone initially attacks the alkene **194** to form a five-membered (primary) ozonide **195**. Due to the differing inductive effects of its substituents, cleavage of this ozonide occurs in a highly regioselective fashion to give a ketone **196** derived from the olefinic carbon bearing the stronger electron-withdrawing group (CH_2OR_2), and a zwitterionic carbonyl oxide **197** arising from the carbon to which is bonded the more electron-donating group (R_1). Nucleophilic attack on **197** by an alcohol yields an alkoxy hydroperoxide **198**, which in the Schreiber modification is acetylated with acetic anhydride to produce **199**. Base mediated elimination from **199** furnishes an ester **200**.[81]



Scheme 47

In accord with expectations based on this mechanism, ozonolysis of diene **190** in the presence of benzyl alcohol gave an intermediate benzyloxyl

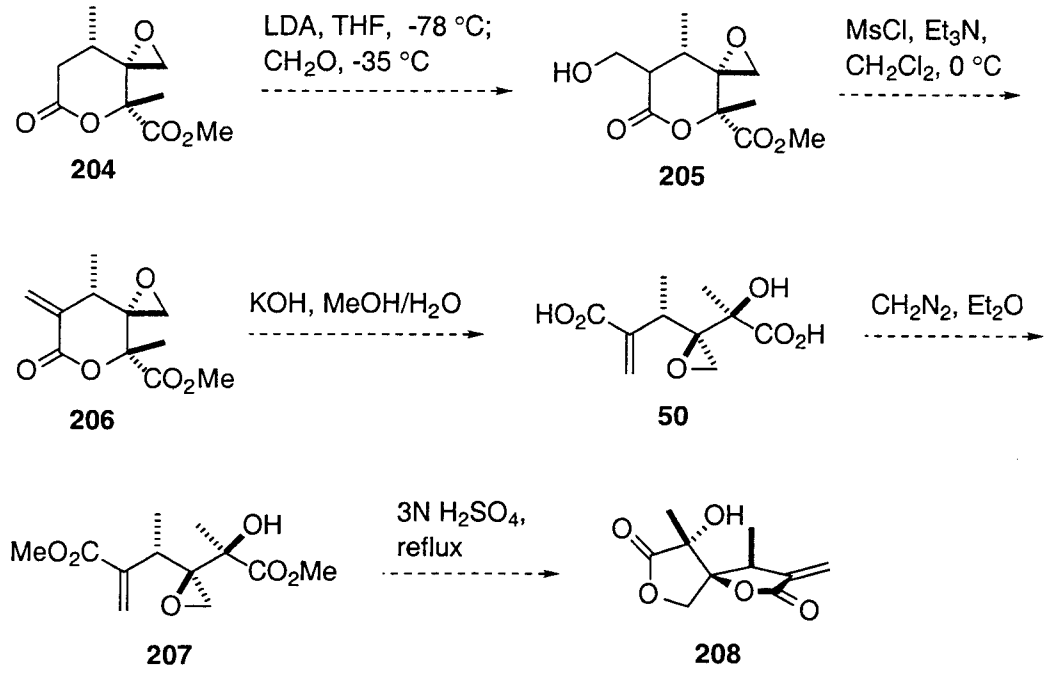
hydroperoxide, which upon treatment with acetic anhydride and triethylamine provided benzyl ester **201**. Without purification, the aldehyde **201** was oxidized to the corresponding carboxylic acid with sodium chlorite, and the acid was converted to its methyl ester **202**. Hydrogenolysis of the benzyl ester was accomplished with 10% palladium on activated carbon under an hydrogen atmosphere and cleanly produced the monocarboxylic acid **203**.[93] The latter was lactonized under Mukaiyama's conditions[89] to afford δ-lactone **204** in excellent overall yield from **202** (**Scheme 48**).



Scheme 48

Thus far, lactone **204** has resisted all attempts at α-methylenation with Eschenmoser's reagent, and a synthesis of swazinecic acid has yet to be completed. Future work will focus on conversion of **204** to β-hydroxy lactone **205** by treatment of the enolate of **205** with gaseous formaldehyde (**Scheme**

49). Exposure of **205** to methanesulfonyl chloride and base should lead directly to *exo* methylene lactone **206** which should undergo basic hydrolysis to provide swazinecic acid (**50**). The latter would first be characterized as its dimethyl ester **207** and then converted with hot sulfuric acid to a spirodilactone. Following the precedent established with **184**, this spirodilactone should possess the structure **208**.



Scheme 49

Although this route to swazinecic acid remains unfinished, it was possible to confirm the structure including absolute configuration of this necic acid independently. An X-ray crystallographic analysis of natural swazine conclusively established its structure as **2** (**Figure 3.3**). The known absolute

configuration[85,94] of the necine portion (retronecine) of **2** mandates that swazinecic acid possesses 2*R*,3*S*,4*S* configuration.

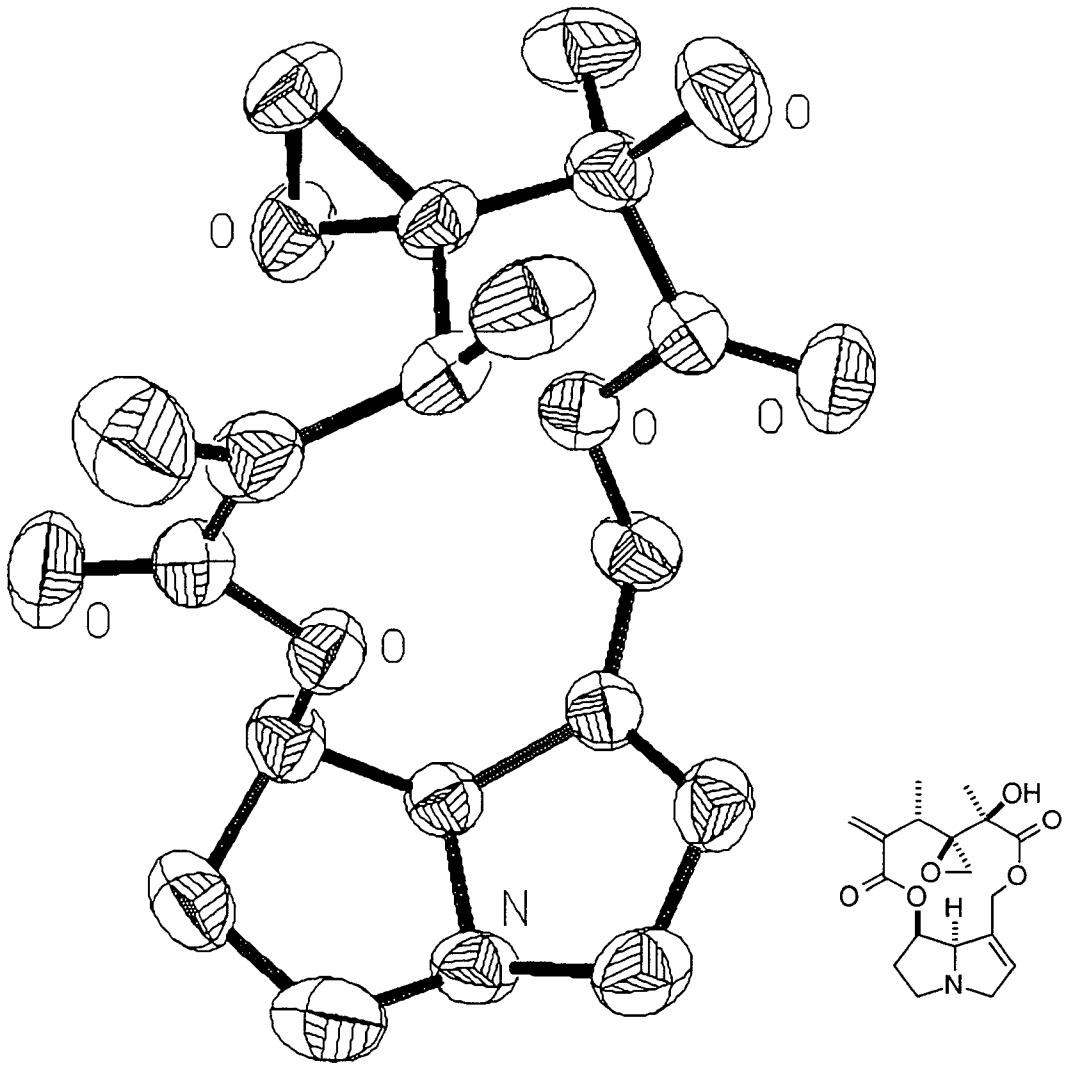


Figure 3.3. ORTEP Diagram from X-ray Crystallographic Analysis of (-)-Swazine (**2**).

In conclusion, this work accomplished the first asymmetric synthesis of 2-*epi*-swazinecic acid (**181**) and significantly extended a general strategy for necic acid synthesis based on the monoterpene citronellal. Although the configuration of the tertiary alcohol at C-2 of **181** is epimeric with that of natural swazinecic acid (**50**), it was shown that this center can be inverted by simply reversing the sequence of Grignard reactions with methyl and vinylmagnesium bromide. The different configuration at the spiro center of **51** and **184** arising from acidic hydrolysis of the parent alkaloid (-)-swazine (**2**) and the dimethyl ester **182** is explained by different reaction mechanisms in each case. Finally, an X-ray crystallographic analysis of natural swazine confirmed that its structure is correctly represented as **2**.

CHAPTER VI

EXPERIMENTAL SECTION

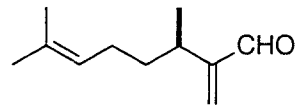
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, acetonitrile and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade. Moisture and air sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame dried under a stream of argon gas, and glass syringes were oven dried at 120 °C and cooled in a desicator over anhydrous calcium sulfate prior to use.

Unless otherwise stated, concentration under reduced pressure (or *in vacuo*) refers to a rotary evaporator at water aspirator pressure.

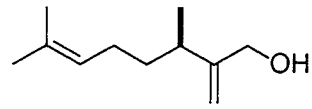
Analytical thin layer chromatography (TLC) was performed using precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light, and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1M sulfuric acid in methanol or 1% solution of potassium permanganate in 2% 1N sodium hydroxide in water. Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM). Radial chromatography was carried out on individually prepared rotors with layer thicknesses of 1, 2, or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, California.

Melting points were measured using a Buchi melting point apparatus, and are uncorrected. Infrared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300 or a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order: chemical shift, number of protons, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad), and coupling constant (*J*) in Hertz (Hz).

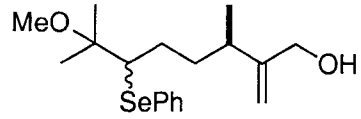
Chemical ionization (CI) high and low resolution mass spectroscopy (HRMS and MS) were obtained using a Kratos MS-50 spectrometer with a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtained using a Varian MAT311 or a Finnegan 4000 spectrometer. X-ray crystallographic data were collected on a Siemens P4 spectrometer and these data were interpreted using the direct methods program contained in the SHELXTL (Silicon Graphics/Unix) software package. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.



α,β-Unsaturated Aldehyde 133. To a stirred solution of diisopropylamine (3.60 mL, 25.6 mmol) in 15 mL of tetrahydrofuran at -78 °C was added *n*-butyllithium (16.1 mL, 24.5 mmol). After being stirred at 0 °C for 15 min, the reaction mixture was cooled to -78 °C and a solution of (*R*)-(+)-citronellal (**102**) (3.44 g, 22.3 mmol) in 15 mL of tetrahydrofuran was added dropwise over 45 min via cannula. The mixture was stirred at -78 °C for 1 h and was then added to a suspension of Eschenmoser's salt (11.6 g, 63.0 mmol) in 30 mL of tetrahydrofuran at -78 °C. After being stirred at -78 °C for 1 h, the suspension was allowed to warm to room temperature and was stirred at that temperature for 5 h. The solvent was removed and a solution of iodomethane (4.2 mL, 67.0 mmol) in 15 mL of methanol was added. After being stirred at 4 °C for 12 h, the reaction mixture was allowed to warm to room temperature and was stirred at that temperature for 5 h. The methanol was removed *in vacuo* and 42 mL of 5% aqueous sodium bicarbonate and 50 mL of dichloromethane was added and the mixture was stirred at room temperature for 16 h. The aqueous layer was separated and was extracted with dichloromethane (5 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to give 3.49 g (94%) of **133**: $[\alpha]_D^{23}$ -9.4° (*c* 20.15, $CHCl_3$); IR (neat) 2950, 1690, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (3H, d, *J* = 7 Hz), 1.40 (1H, m), 1.54 (1H, m), 1.57 (3H, s), 1.67 (3H, s), 1.93 (2H, m), 2.71 (1H, m), 5.08 (1H, m), 5.99 (1H, s), 6.23 (1H, s), 9.53 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6, 19.6, 25.7, 25.8, 31.0, 35.6, 124.2, 131.6, 133.0, 155.5, 194.6; Anal. calcd. for $C_{11}H_{18}O$; C, 79.46; H, 10.91. Found: C, 79.11; H, 10.72.

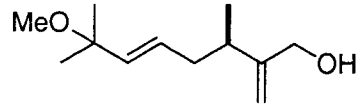


(3*R*)-2-(Hydroxymethyl)-3,7-dimethylocta-1,6-diene (134). To a stirred solution of **133** (3.44 g, 20.7 mmol) and cerium(III) chloride heptahydrate (7.73g, 20.7 mmol) in 50 mL of methanol at 0 °C was added portionwise sodium borohydride (1.02 g, 27.0 mmol). The reaction mixture was stirred for 15 min and was quenched with 50 mL of saturated aqueous ammonium chloride. After removal of methanol *in vacuo*, 150 mL of water was added and was extracted with ethyl acetate (5 x 100 mL). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford 3.23 g (93%) of alcohol **134**: $[\alpha]_D^{23}$ -18.7° (*c* 3.66, $CHCl_3$); IR (neat) 3300 (broad), 2900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (3H, d, *J* = 7 Hz), 1.37 (1H, m), 1.48 (2H, m), 1.59 (3H, s), 1.68 (3H, d, *J* = 1 Hz), 1.96 (2H, m), 2.16 (1H, m), 4.10 (2H, s, br), 4.89 (1H, s), 5.05 (1H, d, *J* = 1 Hz), 5.09 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 20.1, 25.7, 25.9, 35.8, 36.6, 64.5, 107.9, 124.5, 131.5, 153.9; HRMS calcd. for $C_{11}H_{20}O$ *m/z* 168.1514. Found:168.1511. This compound was converted to its 4-phenylbenzoate. Anal. calcd. for $C_{24}H_{28}O_2$: C, 82.71; H, 8.11. Found: C, 82.49; H, 8.25.



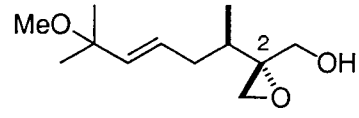
(3*R*)-2-(Hydroxymethyl)-3,7-dimethyl-7-methoxy-6-phenyl-selenyl-1-octene (135). To a stirred solution of **134** (995.4 mg, 5.93 mmol) and sodium bicarbonate (2.84 g, 33.8 mmol) in 30 mL of methanol was added

dropwise a solution of phenylselenenyl chloride (2.74 g, 14.2 mmol) in 30 mL of methanol via cannula. The reaction mixture was stirred at room temperature for 2 h and the methanol was removed *in vacuo*. The resultant suspension was filtered through a small pad of silica gel which was eluted with diethyl ether. The combined filtrates were evaporated, and the residue was purified by chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to provide 2.08 g (99%) of **135** as a diastereomeric mixture: IR (neat) 3396 (broad), 3070, 2971, 1649, 1576, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.02-1.04 (3H, m), 1.24-1.45 (8H, m), 1.76-2.15 (4H, m), 3.04-3.08 (1H, m), 3.14 (3H, s), 4.03 (2H, s, br), 4.85 (1H, d, J = 7 Hz), 5.02-5.04 (1H, m), 7.21-7.26 (3H, m), 7.56-7.59 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 19.7, 20.7, 22.6, 22.8, 23.9, 24.0, 28.8, 34.5, 34.7, 36.5, 36.8, 49.3, 49.4, 57.7, 57.8, 64.3, 78.4, 108.0, 108.4, 126.9, 127.0, 128.9, 131.8, 133.8, 133.9; HRMS calcd. for $C_{18}H_{28}O_2Se$ *m/z* 354.1262. Found: *m/z* 354.1261.



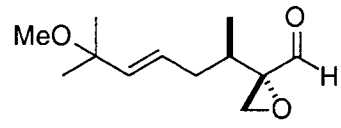
(3*R*)-2-(Hydroxymethyl)-3,7-dimethyl-7-methoxyocta-1,5-diene (136). To a stirred solution of **135** (2.10 g, 5.94 mmol) and sodium bicarbonate (19.5 g, 0.232 mol) in 59 mL of tetrahydrofuran and 59 mL of water was added 59 mL of 30% aqueous hydrogen peroxide solution. The mixture was stirred at room temperature for 30 min and 80 mL of water was added. The mixture was extracted with diethyl ether (6 x 100 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to yield

1.21 g (98%) of **136**: $[\alpha]_D^{23}$ -12.2° (*c* 3.66, $CHCl_3$); IR (neat) 3417, 3248, 2978, 1649, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (3H, d, *J* = 7 Hz), 1.19 (6H, s), 2.00-2.24 (3H, m), 2.45 (1H, s, br), 3.08 (3H, s), 4.04 (2H, s), 4.82 (1H, s), 5.02 (1H, s), 5.32-5.44 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 25.7, 36.5, 38.5, 50.1, 64.6, 74.9, 108.2, 128.3, 136.6, 153.1; HRMS calcd. for $C_{12}H_{22}O_2$ *m/z* 199.1698. Found: *m/z* 199.1698.



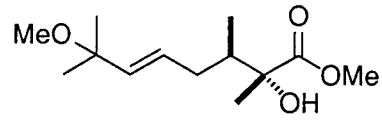
(2*R*,3*R*)-3,7-Dimethyl-7-methoxy-2-oxiranyl-5-octenol (137). To a stirred suspension of 3Å molecular sieves in 25 mL of dichloromethane at -15 °C was added titanium(IV) isopropoxide (2.49 mL, 8.35 mmol) and diisopropyl (-)-tartrate (1.77 mL, 8.35 mmol). The reaction mixture was stirred for 15 min at -15 °C. *tert*-Butyl hydroperoxide (2.23 mL, 11.1 mmol) was added and stirring was continued for 30 min. To this mixture was added a solution of **136** (1.10 g, 5.57 mmol) in 25 mL of dichloromethane via cannula. The mixture was allowed to stir for an additional 15 min at -15 °C and the reaction flask was placed in a -35 °C freezer for 20 h. After addition of 16 mL of 10% aqueous tartaric acid, the reaction mixture was stirred at -15 °C for 30 min, allowed to warm to room temperature, and stirred for 1 h, during which time an additional 50 mL of dichloromethane was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic extracts were combined and the solvent was removed *in vacuo*. The residue was stirred with 16 mL of 1N aqueous sodium hydroxide in 50 mL of diethyl ether at 0 °C for 30 min. Organic phase was separated and the aqueous phase was washed once with 20 mL of dichloromethane. The combined

organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (40% ethyl acetate in hexanes as eluent) to produce 1.02 g (86%) of **137** as 12:1 mixture of oxiranes: $[\alpha]_D^{23}$ +9.5° (*c* 2.19, $CHCl_3$); IR (neat) 3416, 2978, 2882, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (3H, d, *J* = 7.9 Hz), 1.22 (6H, s), 1.63-1.70 (1H, m), 1.82-2.02 (2H, m), 2.16-2.25 (1H, m), 2.61 (1H, d, *J* = 4.7 Hz), 2.88 (1H, d, *J* = 4.7 Hz), 3.11 (3H, s), 3.66 (1H, dd, *J* = 12.3, 8.8 Hz), 3.82 (1H, dd, *J* = 12.3, 3.7 Hz), 5.38-5.53 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 25.8, 35.2, 36.5, 49.4, 50.1, 60.2, 62.0, 74.6, 127.7, 137.3; HRMS calcd. for $C_{12}H_{22}O_3$ *m/z* 213.1490. Found: *m/z* 213.1490.



(2*R*,3*R*)-3,7-Dimethyl-7-methoxy-2-oxiranyl-5-octenal (138). To a stirred solution of oxalyl chloride (624 μL, 7.14 mmol) in 25 mL of dichloromethane at -78 °C was added dimethyl sulfoxide (1.0 mL, 14.3 mmol). The reaction mixture was stirred for 10 min and a solution of **137** (764 mg, 3.57 mmol) in 20 mL of dichloromethane was added via cannula. An additional 5 mL of dichloromethane was used to ensure that all the alcohol was transferred to the reaction flask. The mixture was stirred for 10 min, triethylamine (3.0 mL, 21.4 mmol) was added and stirring was continued for 1 h. The reaction mixture was diluted with 70 mL of diethyl ether and the solution was filtered through a small pad of silica gel. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (17% ethyl acetate in hexanes as eluent) to give 757 mg (100%) of **138**: $[\alpha]_D^{23}$ -9.0° (*c* 2.18, $CHCl_3$); IR (neat) 3525, 2979, 1734, 1253, 1173, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93

(3H, d, J = 7 Hz), 1.23 (6H, s), 1.36 (3H, s), 1.80-2.06 (3H, m), 3.02 (1H, s), 3.13 (3H, s), 3.79 (3H, s), 5.37-5.51 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 2.30, 12.6, 14.1, 23.6, 25.7, 25.9, 33.1, 34.9, 40.9, 50.2, 52.7, 74.7, 128.3, 137.3, 188.9; HRMS calcd. for $C_{12}H_{20}O_3$ $(M - MeOH)^+$ *m/z* 212.1412. Found: *m/z* 212.1412. Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 64.01; H, 10.00.

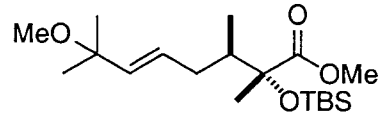


Methyl Ester 141. To a stirred solution of **138** (757 mg, 3.57 mmol) and 2-methyl-2-butene (18 mL) in 70 mL of *tert*-butanol at 0 °C was added dropwise a solution of sodium chlorite (2.95 g, 32.6 mmol) and sodium phosphate monobasic monohydrate (3.00 g, 21.7 mmol) in 45 mL of water. The reaction mixture was stirred for 10 min and was diluted with 100 mL of water. The aqueous layer was separated and was acidified to pH 3 with 10% aqueous hydrochloric acid. The mixture was extracted with dichloromethane (5 x 70 mL), and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 730 mg (90%) of a carboxylic acid.

To a stirred solution of the above acid (250 mg, 1.09 mmol) in 30 mL of tetrahydrofuran at room temperature was added portionwise lithium aluminum hydride (83 mg, 2.19 mmol). The reaction mixture was stirred for 3 h and was then quenched by careful addition of 10 mL of water followed by 10 mL of 1N aqueous sodium hydroxide. After being stirred at room temperature for 5 min, the mixture was acidified to pH 2 with 10% aqueous hydrochloric acid. The mixture was extracted with diethyl ether (5 x 20 mL), and the combined organic

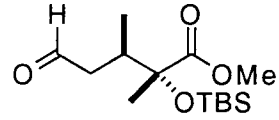
extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*.

A stirred solution of the crude acid in 20 mL of diethyl ether was treated with an ethereal solution of diazomethane[95] until the yellow color persisted. Stirring was continued for 30 min, the solvent was removed *in vacuo*, and the residue was purified by chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to produce 121 mg (45%) of **141**: $[\alpha]_D^{23}$ -9.0° (*c* 2.18, $CHCl_3$): IR (neat) 3525 (broad), 2979, 1734, 1253, 1173, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (3H, d, *J* = 7 Hz), 1.23 (6H, s), 1.36 (3H, s), 1.80-2.06 (3H, m), 3.02 (1H, s), 3.13 (3H, s), 3.79 (3H, s), 5.37-5.51 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 2.30, 12.6, 14.1, 23.6, 25.7, 25.9, 33.1, 34.9, 40.9, 50.2, 52.7, 74.7, 128.3, 137.3, 188.9; HRMS calcd. for $C_{12}H_{20}O_3$ (M - MeOH)$^+$ *m/z* 212.1412. Found: *m/z* 212. 1412. Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 64.01; H, 10.00.



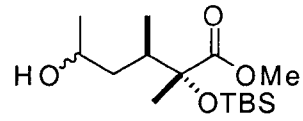
Silyloxy Ester 142. To a stirred solution of **141** (94 mg, 0.384 mmol) in 10 mL of dichloromethane at 0 °C was added triethylamine (534 μL, 3.84 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (440 μL, 1.92 mmol). The reaction mixture was stirred at room temperature for 24 h and was quenched with 7.5 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 x10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5% ethyl

acetate in hexanes as eluent) to yield 113 mg (82%) of **142**: $[\alpha]_D^{23}$ +18.0° (*c* 1.07, $CHCl_3$); IR (neat) 2932, 1750, 1126, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.06 (3H, s), 0.10 (3H, s), 0.85 (3H, d, *J* = 6 Hz), 0.89 (9H, s), 1.24 (6H, s), 1.36 (3H, s), 1.62-1.89 (2H, m), 2.09-2.15 (1H, m), 3.13 (3H, s), 3.70 (3H, s), 5.34-5.52 (2H, m); ^{13}C NMR (CDCl3, 100 MHz) δ -3.3, -2.8, 12.9, 18.6, 23.5, 25.9, 34.9, 42.4, 50.2, 51.7, 74.7, 80.1, 129.0, 136.9, 176.3; HRMS calcd. for $C_{14}H_{25}O_3Si$ $(M - MeOH)^+$ *m/z* 269.1573. Found: *m/z* 269.1573. Anal. calcd. for $C_{19}H_{38}O_4Si$: C, 63.64; H, 10.68; Si, 7.83. Found: C, 63.68; H, 10.70; Si, 7.84.

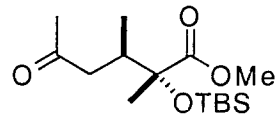


Aldehyde Ester 143. Ozone was passed through a stirred solution of **142** (324 mg, 0.904 mmol) in 65 mL of dichloromethane at -78 °C until a persistent blue color remained. The solution was stirred at -78 °C for 10 min, after which argon was bubbled into the solution until the blue color had dissipated. Methyl sulfide (1.3 mL, 18.1 mmol) was added, and the reaction mixture was allowed to warm to room temperature and was stirred for 1 h at that temperature. Excess methyl sulfide was removed by bubbling argon through the solution for 15 min. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to provide 231 mg (89%) of **143**: $[\alpha]_D^{23}$ +14.6° (*c* 1.59, $CHCl_3$); IR (neat) 2930, 2821, 1747, 1729, 1255, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.06 (3H, s), 0.11 (3H, s), 0.88 (9H, s), 1.95 (3H, d, *J* = 7 Hz), 1.38 (3H, s), 2.20-2.30 (1H, m), 2.43-2.53 (2H, m), 3.70 (3H, s), 9.72 (1H, t, *J* = 1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.5, -2.9, 14.3, 18.5, 22.9, 25.8, 37.10, 46.7, 52.0, 79.5, 175.6,

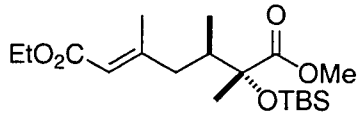
201.9; LRMS *m/z* 229 (20), 203 (20), 171 (50), 113 (17), 89 (27), 75 (86), 73 (100).



Hydroxy Ester 144. To a stirred solution of **143** (24.8 mg, 0.086 mmol) in 10 mL of diethyl ether at -78 °C was added methylmagnesium bromide (144 μL, 3 M, 0.431 mmol). After being stirred for 10 min at -78 °C, the reaction mixture was quenched with 5 mL of water. The mixture was warmed to room temperature, acidified to pH 2 with 10% aqueous hydrochloric acid, and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to give 17.2 mg (66%) of **144** as a diastereomeric mixture and 3.6 mg (15%) of recovered **143**. **144**: IR (neat) 3406 (broad), 2856, 1748, 1193, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 0.91 (3H, d, J = 7 Hz), 1.16 (3H, d, J = 11 Hz), 1.36 (3H, d, J = 4 Hz), 1.25-1.46 (2H, m), 1.59 (1H, s, br), 1.87-2.08 (1H, m), 3.70 (3H, s), 3.77-3.84 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.4, -2.8, 13.5, 14.4, 18.5, 23.1, 23.2, 23.6, 24.6, 25.9, 29.7, 38.8, 39.4, 41.7, 42.0, 51.8, 65.9, 66.6, 80.3, 80.4, 176.3; LRMS *m/z* 247 $(M - C_4H_9)^+$, 217 (36), 187 (82), 155 (20), 145 (21), 119 (34), 113 (70), 95 (28), 89 (40), 75 (100); HRMS calcd. for $C_{11}H_{23}O_4Si$ $(M - C_4H_9)^+$ *m/z* 247.1366. Found: *m/z* 247.1365.

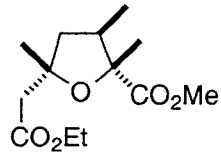


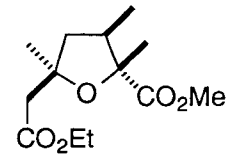
Keto Ester 145. To a stirred solution of oxalyl chloride (17 μL, 0.188 mmol) in 10 mL of dichloromethane at -78 °C was added dimethyl sulfoxide (27 μL, 0.376 mmol). The mixture was stirred at -78 °C for 5 min, and a solution of **144** (29 mg, 94.1 mmol) in 3 mL of dichloromethane was added. Stirring was continued for 10 min, after which triethylamine (79 μL, 0.565 mmol) was added. The solution was stirred for 30 min, and 10 mL of diethyl ether was added. The mixture was filtered through a small pad of silica gel and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel (10% ethyl acetate in hexanes as eluent) to afford 28 mg (100%) of **145**: $[\alpha]_D^{23}$ +6.1° (*c* 2.45, $CHCl_3$); IR (neat) 2955, 2858, 1743, 1720, 1253, 1192, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (3H, s), 0.10 (3H, s), 0.87 (3H, d, *J* = 7 Hz), 0.88 (9H, s), 1.35 (3H, s), 2.10 (3H, s), 2.20 (1H, dd, *J* = 16, 9 Hz), 2.37-2.46 (1H, m), 2.50 (1H, dd, *J* = 16, 3 Hz), 3.67 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.5, -2.9, 14.1, 18.5, 23.4, 25.9, 30.3, 37.8, 46.2, 51.9, 79.4, 175.8, 208.1; LRMS *m/z* 245 [$(M - C_4H_9)^+$, 30], 243 (40), 217 (75), 185 (100); HRMS calcd. for $C_{11}H_{21}O_4Si$ $(M - C_4H_9)^+$ *m/z* 245.1209. Found: *m/z* 245.1210. Anal. calcd. for $C_{15}H_{30}O_4Si$: C, 59.59; H, 10.00. Found: C, 59.60; H, 9.96.



α,β-Unsaturated Ester 146. To a stirred suspension of potassium hydride (83 mg, 0.729 mmol) in 3 mL of tetrahydrofuran at room temperature was added ethyl triethylphosphonoacetate (161 μL, 0.810 mmol). The reaction mixture was stirred for 10 min and a solution of **145** (49 mg, 0.162 mmol) in 1

mL of tetrahydrofuran was added via cannula. An additional 1 mL of tetrahydrofuran was used to ensure that all the ketone was transferred to the reaction flask. The reaction mixture was heated at reflux for 43 h and was quenched with 5 mL of water. The mixture was extracted with diethyl ether (3 x 10 mL), and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to give 30 mg (50%) of **146** as a mixture of *E*- and *Z*- isomers (5.6 : 1 ratio by ^{1}H NMR). The two isomers were separated by chromatography to provide pure *E*- **146**: $[\alpha]_D^{23}$ +14.8° (*c* 3.25, $CHCl_3$); IR (neat) 2953, 2857, 1746, 1717, 1254, 1223, 1192, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (3H, s), 0.83 (3H, s), 0.89 (3H, d, *J* = 1 Hz), 0.90 (9H, s), 1.28 (3H, t, *J* = 7 Hz), 1.37 (3H, s), 1.85-1.93 (1H, m), 2.11 (3H, d, *J* = 1 Hz), 2.03-2.36 (1H, m), 3.71 (3H, s), 4.14 (2H, q, *J* = 7 Hz), 5.64 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -3.4, -2.8, 12.8, 14.3, 18.4, 18.6, 23.5, 25.9, 29.7, 39.9, 43.5, 51.8, 59.5, 80.0, 117.4, 159.0, 166.6, 176.0; LRMS *m/z* 373, 357, 328, 327 (100), 315; HRMS calcd. for $C_{19}H_{37}O_5Si$ $(M + H)^+$ *m/z* 373.2410. Found: *m/z* 373.2411.





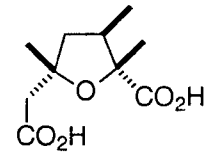
Tetrahydrofurans 148 and 149. A from 146 and 147. To a stirred solution of a mixture of **146** and **147** (29.9 mg, 80.3 μmol) in 5 mL of tetra-*n*-hydrofuran was added tetra-*n*-butylammonium fluoride (803 μL, 0.803 mmol). After being stirred at room temperature for 1 h, the reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on

silica gel (17% ethyl acetate in hexanes as eluent) to provide 16 mg (77%) of a mixture of **148** and **149** (1 : 4.5 ratio by ^{1}H NMR).

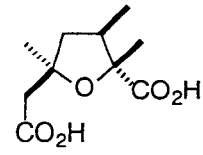
B from 146. To a stirred solution of **146** (40 mg, 0.107 mmol) in 5 mL of tetrahydrofuran was added tetra-*n*-butylammonium fluoride (1.61 mL, 1.61 mmol). After being stirred at room temperature for 1 h, the reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (17% ethyl acetate in hexanes as eluent) to give 20.8 mg (75%) of a mixture of **148** and **149** (1 : 4.5 ratio). The two diastereomers were separated by preparative HPLC (250 x 4.6 mm silica column, 15:1 hexane-ethyl acetate, 3 mL min^{-1}).

148: $[\alpha]_D^{23}$ +11.7° (*c* 0.30, $CHCl_3$); IR (neat) 2977, 1734, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (3H, d, *J* = 7 Hz), 1.26 (3H, t, *J* = 7 Hz), 1.29 (3H, s), 1.43 (3H, s), 1.56 (1H, dd, *J* = 13, 13 Hz), 2.42 (1H, dd, *J* = 13, 7 Hz), 2.54 (1H, d, *J* = 15 Hz), 2.65 (1H, d, *J* = 15 Hz), 2.63-2.73 (1H, m), 3.73 (3H, s), 4.12 (2H, q, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 20.6, 28.2, 40.0, 43.9, 45.4, 52.2, 60.2, 81.5, 85.3, 171.0, 175.4.

149: $[\alpha]_D^{23}$ +33.9° (*c* 1.59, $CHCl_3$); IR (neat) 2977, 1734, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (3H, d, *J* = 7 Hz), 1.25 (3H, s), 1.26 (3H, t, *J* = 7 Hz), 1.34 (3H, s), 1.92 (1H, dd, *J* = 12, 12 Hz), 2.05 (1H, dd, *J* = 13, 7 Hz), 2.56 (1H, d, *J* = 14 Hz), 2.69 (1H, d, *J* = 14 Hz), 2.65-2.75 (1H, m), 3.73 (3H, s), 4.12 (2H, q, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 14.2, 20.3, 26.9, 39.9, 43.9, 47.5, 52.2, 60.3, 81.2, 85.2, 170.8, 175.6; LRMS *m/z* 259, 199 (100), 171; HRMS calcd. for $C_{13}H_{22}O_5$ $(M + H)^+$ *m/z* 259.1546. Found: *m/z* 259.1545.

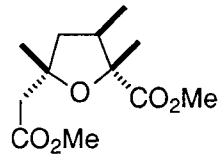


(+)-Nemorensic Acid (25). To a stirred solution of **148** (3 mg, 11.6 μmol) in 1 mL of tetrahydrofuran was added 200 μL of lithium hydroxide (1M). After being stirred at room temperature for 3 h, the reaction mixture was quenched with 2 mL of water and was acidified to pH 2 with 10% aqueous hydrochloric acid. The mixture was extracted with diethyl ether (4 x 2 mL) and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to produce 2.4 mg (91%) of **25** as a yellow crystalline solid which showed identical spectral properties to those reported for the natural product: $[\alpha]_D^{23}$ +87.2° (*c* 0.24, EtOH); m.p. 174-175 °C; IR (neat) 3550-3100 (broad), 2925, 2860, 1722, 1630, 1461, 1383, 1124, 1085, 1038 cm^{-1}; ^1H NMR [$(CD_3)_2SO$, 400 MHz] δ 0.99 (3H, d, *J* = 7 Hz), 1.13 (3H, s), 1.27 (3H, s), 1.50 (1H, dd, *J* = 12, 12 Hz), 2.10 (1H, dd, *J* = 13, 7 Hz), 2.30 (1H, d, *J* = 14 Hz), 2.46 (1H, d, *J* = 14 Hz), 2.45-2.55 (1H, m).

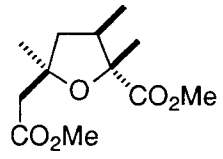


(+)-**Isonemorensic Acid (153)**. To a stirred solution of **149** (15 mg, 58.1 mmol) in 2 mL of tetrahydrofuran was added 1 mL of lithium hydroxide (1M). After being stirred at room temperature for 3 h, the reaction mixture was quenched with 5 mL of water and was acidified to pH 2 with 10% aqueous hydrochloric acid. The mixture was extracted with diethyl ether (4 x 5 mL) and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to produce 12.5 mg

(94%) of **153**: $[\alpha]_D^{23}$ +55.4° (*c* 0.99, $CHCl_3$); IR (neat) 3640-3050 (broad), 2971, 2919, 1713, 1378, 1121, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (3H, d, *J* = 7 Hz), 1.26 (1H, s), 1.32 (3H, s), 1.43 (3H, s), 1.91 (1H, dd, *J* = 13, 13 Hz), 2.14 (1H, dd, *J* = 13, 7 Hz), 2.65 (1H, d, *J* = 15 Hz), 2.74 (1H, d, *J* = 15 Hz), 2.61-2.78 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 19.6, 26.9, 40.0, 44.4, 47.1, 81.6, 85.5, 175.8, 177.5.

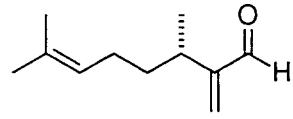


Dimethyl Nemorensate (154). To a stirred solution of **25** (2.5 mg, 0.012 mmol) in 0.5 mL of diethyl ether was added an ethereal solution of diazomethane[95] until a yellow color persisted. After being stirred at room temperature for 30 min, the reaction mixture was concentrated *in vacuo* to yield 2.8 mg (100%) of **154**: IR (neat) 2946, 2863, 1734, 1447, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (3H, d, *J* = 7 Hz), 1.29 (3H, s), 1.43 (3H, s), 1.56 (1H, dd, *J* = 12, 12 Hz), 2.40 (1H, dd, *J* = 13, 7 Hz), 2.56 (1H, d, *J* = 14 Hz), 2.66 (1H, d, *J* = 15 Hz), 2.61-2.71 (1H, m), 3.66 (3H, s), 3.73 (3H, s).



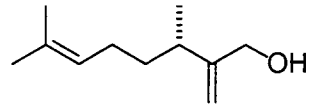
Dimethyl Isonemorensate (155). To a stirred solution of **153** (10 mg, 0.046 mmol) in 1 mL of diethyl ether was added an ethereal solution of diazomethane[95] until a yellow color persisted. After being stirred at room temperature for 30 min, the reaction mixture was concentrated *in vacuo* to give

11.3 mg (100%) of **155**: $[\alpha]_D^{23}$ +45.8° (*c* 0.28, $CHCl_3$); IR (neat) 2956, 1733, 1440, 1383, 1346, 1242, 1213, 1118, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (3H, d, *J* = 7 Hz), 1.24 (3H, s), 1.34 (3H, s), 1.92 (1H, dd, *J* = 13, 13 Hz), 2.05 (1H, dd, *J* = 13, 7 Hz), 2.58 (1H, d, *J* = 14 Hz), 2.71 (1H, d, *J* = 14 Hz), 2.64-2.77 (1H, m), 3.66 (3H, s), 3.74 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 20.3, 27.0, 39.9, 43.8, 47.2, 51.5, 52.3, 81.2, 85.2, 171.3, 175.6; LRMS *m/z* 245, 185 (100) 171; HRMS calcd. for $C_{12}H_{20}O_5$ $(M + H)^+$ *m/z* 245.1389. Found: *m/z* 245.1389.



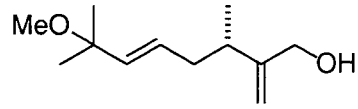
α,β-Unsaturated Aldehyde 158. To a stirred solution of diisopropylamine (2.09 mL, 14.9 mmol) in 15 mL of tetrahydrofuran at -78 °C was added *n*-butyllithium (8.92 mL, 14.3 mmol). After being stirred at 0 °C for 15 min, the reaction mixture was cooled to -78 °C and a solution of (*S*)-(-)-citronellal (**157**) (2.0 g, 13.0 mmol) in 15 mL of tetrahydrofuran was added dropwise over 30 min. An additional 5 mL of tetrahydrofuran was used to ensure that all of the citronellal was transferred to the reaction flask. The mixture was stirred at -78 °C for 1 h and was added to a stirred suspension of Eschenmoser's salt (3.60 g, 19.46 mmol) in 20 mL of tetrahydrofuran at -78 °C. The suspension was allowed to stir for 1 h at -78 °C and for 5 h at room temperature. After most of the solvent was removed, a solution of iodomethane (1.62 mL, 25.94 mmol) in 30 mL of methanol was added to the residue and the solution was stirred at room temperature for 12 h. The solvent was evaporated, and 26 mL of 5% aqueous sodium bicarbonate and 30 mL of dichloromethane was added to the residue. The mixture was stirred at room temperature for 5 h,

the organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to yield 1.93 g (90%) of **158**: $[\alpha]_D^{23}$ +8.4° (*c* 11.8, $CHCl_3$); IR (neat) 2968, 2924, 2859, 2697, 1701, 1458, 1382, 1257, 949 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (3H, d, *J* = 7 Hz), 1.26-1.60 (2H, m), 1.56 (3H, s), 1.67 (3H, d, *J* = 1 Hz), 1.86-1.97 (2H, m), 2.65-2.76 (1H, m), 5.05-5.10 (1H, m), 5.99 (1H, s), 6.23 (1H, s), 9.53 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.5, 19.4, 25.55, 25.65, 30.9, 35.5, 124.0, 131.5, 132.9, 155.4, 194.5; LRMS *m/z* 166 (M^+, 20), 151 (20), 123 (20), 109 (100), 95 (40), 93 (20), 84 (30), 81 (50), 79 (20), 69 (80); HRMS calcd. for $C_{11}H_{18}O$ *m/z* 166.1358. Found: *m/z* 166.1358.



(3*S*)-2-(Hydroxymethyl)-3,7-dimethylocta-1,6-diene (159). To a stirred solution of **158** (1.81 g, 10.9 mmol) and cerium(III) chloride heptahydrate (5.39 g, 14.5 mmol) in 50 mL of methanol at 0 °C was added portionwise sodium borohydride (549 mg, 14.2 mmol). The reaction mixture was stirred for 10 min and was quenched with 50 mL of saturated aqueous ammonium chloride solution. After removal of the methanol, 150 mL of water was added and was extracted with ethyl acetate (4 x 50 mL). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (17% ethyl acetate in hexanes as eluent) to provide 1.70 g (93%) of **159**: $[\alpha]_D^{23}$ +17.6° (*c* 13.09, $CHCl_3$); IR (neat) 3350

(broad), 2964, 2918, 2858, 1661, 1450, 1390, 1239, 1033, 912, 836, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (3H, d, *J* = 7 Hz), 1.22-1.55 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.91-2.03 (2H, m), 2.12-2.21 (1H, m), 2.52 (1H, s, broad), 4.06 (2H, s), 4.87 (1H, s), 5.05-5.11 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.5, 19.9, 25.5, 25.7, 35.7, 36.4, 64.3, 107.6, 124.4, 131.2, 153.7; LRMS *m/z* 168 (20), 151 (30), 150 (30), 149 (25), 137 (60), 135 (60), 109 (40), 107 (25), 95 (100); HRMS calcd. for $C_{11}H_{20}O$ *m/z* 168.1514. Found: *m/z* 168.1515.



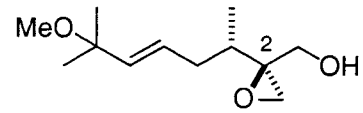
(3*S*)-2-(Hydroxymethyl)-3,7-dimethyl-7-methoxyocta-1,5-diene (160). A. Stepwise Procedure. To a stirred solution of **159** (978 mg, 5.82 mmol) and sodium bicarbonate (2.93 g, 34.9 mmol) in 20 mL of methanol was added a solution of phenylselenenyl chloride (2.96 g, 15.5 mmol) in 50 mL of methanol dropwise *via* cannula. After being stirred at room temperature for 1.5 h, the solution was concentracted and the residue was purified by chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to yield 1.98 g (96%) of a stereoisomeric mixture of methoxyselenides: IR (neat) 3415 (broad), 3070, 2973, 2932, 2870, 2829, 1586, 1483, 1457, 1442, 1380, 1360, 1226, 1129, 1067, 1031, 903, 744, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (3H, d, *J* = 6.9 Hz), 1.24 (3H, s), 1.29 (3H, s), 1.39-1.44 (2H, m), 1.92-1.99 (2H, m), 2.13-2.17 (2H, m), 3.07 (1H, d, *J* = 8.6 Hz), 3.14 (3H, s), 4.06 (2H, s), 4.86 (1H, s), 5.04 (1H, d, *J* = 1.3 Hz), 7.21-7.27 (3H, m), 7.55-7.59 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 22.6, 24.0, 28.8, 34.5, 36.8, 49.3, 57.8, 64.3, 78.5, 108.4, 126.9, 128.9. 133.8, 153.7; LRMS *m/z* 356 (M^+, 60), 339 (60),

284 (20), 167 (100), 149 (100), 123 (20), 111 (20), 107 (30), 95 (20), 93 (20); HRMS calcd. for $C_{18}H_{28}O_2Se$ *m/z* 356.1255. Found: *m/z* 356.1252.

To a stirred suspension of the above methoxyselenides (1.98 g, 5.56 mmol) and sodium bicarbonate (4.66g, 55.5 mmol) in 30 mL of tetrahydrofuran was added 1.26 mL of 30% aqueous hydrogen peroxide. After being stirred for 30 min, the solution was concentracted and 100 mL of water was added. The mixture was extracted with diethyl ether (5 x 30 mL) and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to give 864.9 mg (79%) of **160**: $[\alpha]_D^{23}$ +9.5° (*c* 9.03, $CHCl_3$); IR (neat) 3389 (broad), 2974, 2935, 1459, 1376, 1264, 1176, 1079, 981, 907 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (3H, m), 1.19 (3H, s), 1.20 (3H, s), 1.78-2.16 (2H, m), 2.17-2.22 (2H, m), 2.22-2.51 (1H, broad), 3.08 (3H, s), 4.05 (2H, s), 4.84 (1H, d, *J* = 1 Hz), 5.03 (1H, m), 5.34-5.54 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 25.7, 36.5, 38.5, 50.1, 64.6, 74.9, 108.2, 128.3, 136.6, 153.1; LRMS *m/z* 183 [$(M - CH_3)^+$, 20], 167 (40), 151 (40), 149 (80), 123 (20), 113 (20), 111 (100), 109 (30), 107 (20), 93 (40); HRMS calcd. for $C_{11}H_{19}O_2$ $(M - CH_3)^+$ *m/z* 183.1385. Found: *m/z* 183.1385.

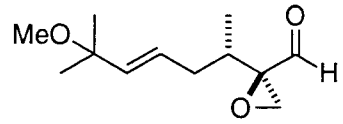
B. Single Step Procedure. To a stirred suspension of alcohol **159** (3.51 g, 20.9 mmol) and sodium bicarbonate (10.52 g, 0.125 mol) in 100 mL of methanol at room temperature was added portionwise phenylselenenyl chloride (4.40 g, 23.0 mmol). After being stirred for 10 min, the reaction mixture was concentrated and 50 mL of tetrahydrofuran and 5.90 mL of 30% aqueous hydrogen peroxide was added. The mixture was stirred at room temperature for 30 min and 80 mL of water was added. The mixture was extracted with ethyl acetate (5 x 30 mL) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue

was purified by chromatography on silica gel (25% ethyl acetate in hexanes as eluent) to give 3.46 g (84%) of **160**.



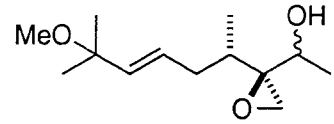
(2*S*,3*S*)-3,7-Dimethyl-7-methoxy-2-oxiranyl-5-octenol (161). To a stirred suspension of 3Å molecular sieve in 30 mL of dichloromethane at room temperature was added titanium(IV) isopropoxide (2.60 mL, 8.73 mmol). The mixture was cooled to -35 °C and diisopropyl (+)-tartrate (2.20 mL, 10.5 mmol) was added. After 15 min, *tert*-butylhydroperoxide (5.24 mL, 26.2 mmol) was added to the stirred mixture and stirring was continued for 15 min. To this mixture was added a solution of **160** (3.46 g, 17.5 mmol) in 10 mL of dichloromethane. An additional 5 mL of dichloromethane was used to ensure that all of the alcohol was transferred to the reaction flask, which was then placed in a -35 °C freezer for 20 h. To the mixture was added 30 mL of 10% aqueous tartaric acid and the mixture was stirred at -35 °C for 30 min and then at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (40% ethyl acetate in hexanes as eluent) to afford 3.27 g (87%) of **161** as a mixture of two diastereomers (13:1 ratio as shown by ^{13}C NMR): $[\alpha]_D^{23}$ -8.3° (*c* 3.46, $CHCl_3$); IR (neat) 3433 (broad), 2976, 2930, 2824, 1463, 1382, 1179, 1153, 1082, 981 cm^{-1}; Major isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (3H, d, *J* = 7 Hz), 1.24 (6H, s), 1.64-1.77 (1H, m), 1.85-1.95 (1H, m), 2.20-2.28 (1H, m), 2.36-2.47 (1H, m), 2.64 (1H, d, *J* = 5 Hz), 2.90 (1H, d, *J* = 5 Hz), 3.14 (3H, s), 3.68 (1H, dd, *J* =

12, 8 Hz), 3.84 (1H, dd, J = 12, 2 Hz), 5.39-5.56 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 25.6, 25.7, 35.1, 36.3, 49.3, 50.1, 60.2, 62.0, 74.6, 127.7, 137.1; LRMS *m/z* 199 [(M - CH_3)$^+$, 20], 183 (30), 167 (20), 165 (20), 137 (20), 113 (20), 109 (100); HRMS calcd. for $C_{11}H_{19}O_3$ (M - CH_3)$^+$ *m/z* 199.1334. Found: *m/z* 199.1335.



(2*S*,3*S*)-3,7-Dimethyl-7-methoxy-2-oxiranyl-5-octenal (162). To a stirred solution of oxalyl chloride (554 μL, 6.35 mmol) in 20 mL of dichloromethane at -78 °C was added dimethyl sulfoxide (900 μL, 12.7 mmol). The mixture was stirred for 15 min and a solution of **161** (680 mg, 3.18 mmol)in 5 mL of dichloromethane was added via cannula. An additional 5 mL of dichloromethane was used to ensure that all of **161** was transferred to the reaction flask. The reaction mixture was stirred at -78 °C for 30 min and triethylamine (2.65 mL, 19.1 mmol) was added. After being stirred at -78 °C for 1 h, the reaction mixture was diluted with 30 mL of diethyl ether and the solution was filtered through a small pad of silica gel, eluting with diethyl ether. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (17% ethyl acetate in hexanes as eluent) to give 673 mg (100%) of **162**: $[\alpha]_D^{23}$ +22.3° (*c* 2.32, $CHCl_3$); IR (neat) 2979, 2940, 2823, 1733, 1465, 1386, 1181, 1084, 986, 859 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (3H, d, J = 7 Hz), 1.24 (6H, s), 2.01-2.36 (3H, m), 2.96 (1H, d, J = 5 Hz), 3.04 (1H, d, J = 5 Hz), 3.13 (3H, s), 5.42-5.49 (2H, m), 8.87 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 25.7, 25.9, 32.0, 35.2, 48.7, 50.2, 63.7, 74.6, 127.6, 137.7, 199.1; LRMS *m/z* 211 (M - H)$^+$, 197 (100), 181 (60), 151 (20), 135

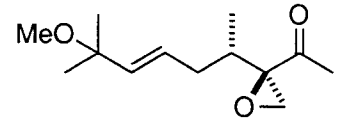
(40), 123 (20), 113 (40), 107 (20), 95 (20); HRMS calcd. for $C_{12}H_{19}O_3$ $(M - H)^+$ *m/z* 211.1334, $C_{11}H_{17}O_3$ $(M - CH_3)^+$ *m/z* 197.1178. Found: *m/z* 211.1334, *m/z* 197.1178.



Alcohol 163. A. From 162. To a stirred solution of **162** (673.5 mg, 3.18 mmol) in 30 mL of tetrahydrofuran at -78 °C was added dropwise a solution of methylmagnesium bromide (2.12 mL, 3M, 6.35 mmol) in 10 mL of tetrahydrofuran via cannula. The reaction mixture was stirred at -78 °C for 2 h and was quenched with 50 mL of water. The mixture was acidified to pH 2 with 10% aqueous hydrochloric acid and was extracted with diethyl ether (4 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (17% ethyl acetate in hexanes followed by 33% ethyl acetate in hexanes as eluent) to afford 451.5 mg (62%) of **163** as a mixture of two diastereomers and183.9 mg (27%) of recovered **162**. **163**: IR (neat) 3445 (broad), 2973, 2937, 1463, 1381, 1268, 1175, 1078, 985, 939 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (3H, d, *J* = 7 Hz), 1.25 (6H, s), 1.25-1.28 (3H, m), 1.67-1.74 (2H, m), 1.90-2.02 (1H, m), 2.23-2.28 (1H, m), 2.64 (1H, d, *J* = 5 Hz), 2.88 (1H, d, *J* = 5 Hz), 3.14 (3H, s), 3.88-3.97 (1H, m), 5.46-5.52 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.8, 19.1, 25.7, 25.9, 33.3, 34.5, 47.6, 50.2, 64.7, 67.4, 74.7, 128.4, 137.1; LRMS *m/z* 213 [$(M - CH_3)^+$, 20], 197 (50), 181 (80), 179 (60), 167 (20), 161 (20), 153 (30), 151 (50), 109 (100), 85 (20), 73 (20); HRMS calcd. for $C_{13}H_{25}O_3$ $(M + H)^+$ *m/z* 229.1804, $C_{12}H_{21}O_3$ $(M - CH_3)^+$ *m/z* 213.1491. Found: *m/z* 229.1800, *m/z* 213.1480.

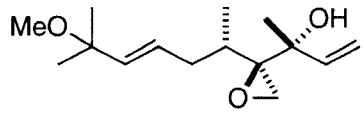
B. From 161. To a stirred solution of **161** (1.02 g, 4.76 mmol) in 30 mL of dichloromethane was added Dess-Martin's periodinane (3.0 g, 7.14 mmol). After being stirred for 1 h, the reaction mixture was diluted with 100 mL of diethyl ether, and 40 mL of 1N aqueous sodium hydroxide was added. The mixture was stirred until both the organic and aqueous layers were clear and colorless. The layers were separated and the organic layer was washed with 20 mL of 1N aqueous sodium hydroxide followed by 20 mL of brine. The organic solution was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*.

To a stirred solution of the residue obtained above in 60 mL of tetrahydrofuran at -78 °C was added methylmagnesium bromide (5.3 mL, 3.0M, 14.3 mmol). After being stirred at -78 °C for 30 min, the reaction mixture was allowed to slowly warm to room temperature over 30 min and was quenched with 100 mL of water. The mixture was acidified to pH 3 with 10% aqueous hydrochloric acid and was extracted with diethyl ether (4 x 30 mL). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (33% ethyl acetate in hexanes as eluent) to provide 859 mg (79%) of **163** as a mixture of two diastereomers and 105 mg (10%) of recovered **161**.



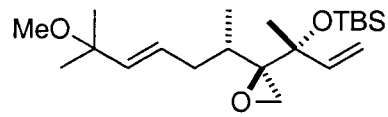
Ketone 164. To a stirred solution of **163** (847.2 mg, 3.72 mmol) in 50 mL of dichloromethane at room temperature was added Dess-Martin's periodinane (3.15 g, 7.43 mmol). After being stirred for 3 h, the reaction mixture

was diluted with 100 mL of diethyl ether, and 40 mL of 1N aqueous sodium hydroxide. The mixture was stirred until both the organic and aqueous phases were clear and colorless. The organic layer was separated and was washed with 20 mL of 1N aqueous sodium hydroxide followed by 20 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (14% ethyl acetate in hexanes as eluent) to give 797.7 mg (95%) of **164**: $[\alpha]_D^{23}$ +27.0° (*c* 3.18, $CHCl_3$); IR (neat) 2978, 2932, 2824, 1715, 1463, 1365, 1263, 1175, 1073, 980, 852 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, d, *J* = 7 Hz), 1.23 (6H, s), 2.0-2.1 (1H, m), 2.03 (3H, s), 2.22-2.35 (2H, m), 2.82 (1H, d, *J* = 5 Hz), 2.92 (1H, d, *J* = 5 Hz), 3.13 (3H, s), 5.46-5.49 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.6, 24.6, 25.6, 25.9, 33.1, 36.0, 49.3, 50.1, 65.1, 74.6, 127.9, 137.3, 208.1; LRMS *m/z* 211 [$(M - CH_3)^+$, 100], 195 (100), 177 (90), 163 (40), 151 (20), 135 (80), 119 (20), 109 (60), 99 (20), 93 (20), 85 (20), 73 (30); HRMS calcd. for $C_{13}H_{21}O_3$ $(M - H)^+$ *m/z* 225.1491, $C_{12}H_{19}O_3$ $(M - CH_3)^+$ *m/z* 211.1334. Found: *m/z* 225.1491, 211.1334.



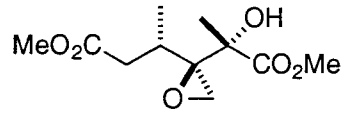
Alcohol 167. To a stirred solution of **164** (797.7 mg, 3.53 mmol) in 60 mL of tetrahydrofuran at -78 °C was added dropwise vinylmagnesium bromide (11.1 mL, 1M, 11.1 mmol). The reaction mixture was stirred at -78 °C for 1 h and was then quenched with 100 mL of water. The mixture was extracted with ethyl acetate (5 x 30 mL), and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (25% ethyl acetate in

hexanes as eluent) to produce 791.8 mg (88%) of **167**: $[\alpha]_D^{23}$ +3.3° (*c* 6.11, $CHCl_3$); IR (neat) 3450 (broad), 2978, 2957, 1453, 1376, 1165, 1078, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (3H, d, *J* = 7 Hz), 1.24 (6H, s), 1.34 (3H, s), 1.59-1.68 (1H, m), 2.04-2.19 (2H, m), 2.34 (1H, s), 2.60 (1H, d, *J* = 5 Hz), 2.95 (1H, d, *J* = 5 Hz), 3.13 (3H, s), 5.19 (1H, dd, *J* = 11, 1 Hz), 5.33 (1H, dd, *J* = 17, 1 Hz), 5.37-5.55 (2H, m), 5.99 (1H, dd, *J* = 17, 11 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 23.5, 26.3, 26.4, 32.2, 35.9, 47.0, 50.7, 67.3, 73.5, 75.3, 114.8, 129.3, 137.4, 141.7; LRMS *m/z* 223 (40), 205 (20), 193 (20), 125 (30), 109 (100), 73 (20); HRMS calcd. for $C_{14}H_{23}O_3$ $(M - CH_3)^+$ *m/z* 239.1647. Found: *m/z* 239.1648.



Silyl Ether 168. To a stirred solution of **167** (1.18 g, 4.64 mmol) in 35 mL of dichloromethane at -40 °C was added 2,6-lutidine (1.10 mL, 9.28 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.6 mL, 6.96 mmol). After being stirred at -40 °C for 1 h, the reaction mixture was allowed to warm to 4 °C. After stirring at this temperature for 14 h, the reaction mixture was quenched with 20 mL of saturated aqueous sodium bicarbonate. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (9% ethyl acetate in hexanes as eluent) to give 1.41 g (83%) of **168**: $[\alpha]_D^{23}$ +5.1° (*c* 6.66, $CHCl_3$); IR (neat) 2958, 2939, 2896, 2858, 2827, 1469, 1369, 1251, 1208, 1177, 1146, 1084, 1047, 985, 929, 836, 786, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (6H, d, *J* = 8 Hz),

0.90 (9H, s), 0.92 (3H, d, J = 7 Hz), 1.24 (6H, s), 1.30 (3H, s), 1.53-1.57 (1H, m), 2.13-2.21 (2H, m), 2.50 (1H, d, J = 5 Hz), 2.77 (1H, d, J = 5 Hz), 3.13 (3H, s), 5.13 (1H, dd, J = 11, 1 Hz), 5.27 (1H, dd, J = 17, 1 Hz), 5.35-5.49 (2H, m), 5.88 (1H, dd, J = 17, 11 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -2.2, -2.1, 18.4, 19.5, 22.7, 25.8, 25.9, 26.0, 30.9, 35.3, 46.4, 50.2, 66.3, 74.7, 114.1, 129.2, 136.4, 142.4; LRMS *m/z* 353 [$(M - CH_3)^+$, 10], 337 (50), 307 (20), 279 (20), 225 (20), 197 (20), 187 (20), 185 (100), 171 (20), 109 (60), 75 (40); HRMS calcd. for $C_{20}H_{37}O_3Si$ $(M - CH_3)^+$ *m/z* 353.2512. Found: *m/z* 353.2511.



Dimethyl Ester 172. Ozone was passed through a stirred suspension of **168** (331.8 mg, 0.898 mmol) and sodium bicarbonate (75.4 mg, 0.898 mmol) in 20 mL of dichloromethane and 4 mL of methanol at -78 °C until a blue color persisted. After being stirred at -78 °C for 5 min, the reaction mixture was allowed to warm to room temperature while argon was passed through the solution until it was clear and colorless. To the reaction mixture was added triethylamine (751 μL, 5.39 mmol) and the acetic anhydride (508 μL, 5.39 mmol), and the mixture was stirred at room temperature for 30 min. To this mixture was added 10 mL of saturated aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate (4 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* .

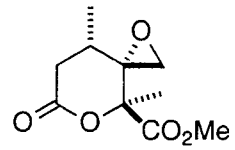
To a stirred solution of the residue obtained above and 2-methyl-2-butene (1.9 mL) in 10 mL of *tert*-butanol at 0 °C was added dropwise a solution of sodium chlorite (744 mg, 8.23 mmol) and sodium phosphate monobasic

monohydrate (744 mg) in 4 mL of water. The reaction mixture was allowed to warm to room temperature and was stirred at that temperature for 30 min, after which 10 mL of brine was added and the organic layer was separated. The aqueous layer was washed once with 10 mL of hexane and was kept for further treatment.

The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was diluted with 10 mL of diethyl ether and an ethereal solution of diazomethane[95] was added until a yellow color persisted. The reaction mixture was stirred at room temperature for 30 min and the solvent was removed *in vacuo*. The residue was purified by chromatography (50% ethyl acetate in hexanes as eluent) to provide 49.9 mg of **172**.

The aqueous layer obtained above was acidified to pH 3 with 10% aqueous hydrochloric acid and was extracted with ethyl acetate (5 x 10 mL). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was diluted with diethyl ether and an ethereal solution of diazomethane[95] was added until a yellow color persisted. The reaction mixture was stirred at room temperature for 30 min, and the solvent was removed *in vacuo* to give an additional 131.2 mg (total 181 mg, 82%) of **172**: $[\alpha]_D^{23}$ -6.42° (*c* 1.87, $CHCl_3$); IR (neat) 3481 (broad), 2952, 1740, 1442, 1370, 1263, 1160, 1098, 1006, 944 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (3H, d, *J* = 7 Hz), 1.44 (3H, s), 1.96-2.04 (1H, m), 2.17-2.22 (1H, m), 2.60 (1H, d, *J* = 4 Hz), 2.77-2.88 (1H, m), 2.93 (1H, d, *J* = 4 Hz), 3.53 (1H, s), 3.66 (3H, s), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 21.3, 28.0, 36.7, 46.0, 51.6, 52.8, 64.4, 75.3, 173.0, 174.3; LRMS *m/z* 247 [$(M + H)^+$, 20], 229 (40), 215 (60), 211 (20), 197 (90), 187 (50), 185 (20), 169

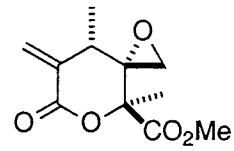
(40), 165 (100), 155 (70), 143 (80), 127 (30), 113 (70), 112 (20), 85 (20), 69 (20); HRMS calcd for $C_{11}H_{19}O_6$ $(M + H)^+$ *m/z* 247.1181. Found: *m/z* 247.1182.



δ-Lactone 178. To a stirred solution of **172** (98 mg, 0.398 mmol) in 1 mL of methanol and 1 mL of water at room temperature was added 0.5M aqueous potassium hydroxide (796 μL, 0.398 mmol). After being stirred at room temperature for 24 h, the reaction mixture was diluted with 2 mL of brine and was acidified to pH 3 with 3% aqueous phosphoric acid. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude carboxylic acid alcohol **177**.

To a stirred solution of 2-chloro-1-methylpyridinium iodide (276.7 mg, 1.08 mmol) and 4-dimethylaminopyridine (220.5 mg, 1.81 mmol) in 4 mL of acetonitrile was added a solution of crude **177** in 2 mL of acetonitrile via cannula. An additional 2 mL of acetonitrile was used to ensure that all of the acid was transferred to the reaction flask. The resulting suspension was stirred for 24 h at room temperature and was filtered through a small pad of silica gel which was washed with diethyl ether. The combined filtrates were concentrated and the residue was purified by chromatography on silica gel (50% ethyl acetate in hexanes as eluent) to provide 72.3 mg (85%) of **178**: $[\alpha]_D^{23}$ +71.8° (*c* 4.81, $CHCl_3$); IR (neat) 2969, 1753, 1450, 1264, 1237, 1119, 998, 948, 843, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (3H, d, *J* = 6 Hz), 1.44 (3H, s), 2.38-2.46 (2H, m), 2.65-2.80 (1H, m), 2.99 (2H, m), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$,

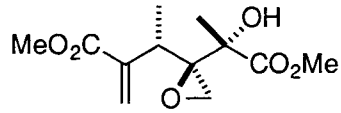
75 MHz) δ 13.3, 18.7, 27.2, 35.9, 47.8, 53.4, 58.4, 85.3, 168.4, 171.3; LRMS *m/z* 215 [(M + H)$^+$, 20], 197 (20), 169 (80), 165 (20), 155 (100), 153 (20), 127 (20), 113 (90); HRMS calcd. for $C_{10}H_{15}O_5$ (M + H)$^+$ *m/z* 215.0920. Found: *m/z* 215.0919.



α-Methylene δ-Lactone 180. To a stirred solution of diisopropylamine (116 μL, 0.885 mmol) in 1 mL of tetrahydrofuran at -78 °C was added *n*-butyllithium (731 μL, 0.870 mmol). After warming to 0 °C for 30 min, the reaction mixture was recooled to -78 °C and a solution of **178** (62.1 mg, 0.290 mmol) in 1.5 mL of tetrahydrofuran was added during 10 min. An additional 1 mL of tetrahydrofuran was used to ensure that all the lactone was transferred to the reaction flask. The reaction mixture was stirred at -78 °C for 45 min and was then stirred at -35 °C. Gaseous formaldehyde, produced by heating paraformaldehyde at 180 °C, was passed through the solution in a stream of argon for 5 min. The reaction mixture was stirred for an additional 5 min at -35 °C and was quenched with 2 mL of saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (3 x 10 mL), and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (67% ethyl acetate in hexanes as eluent) to yield 31.2 mg (44%) of **179** as a mixture of two diastereomers.

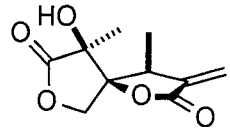
To a stirred solution of **179** (8.4 mg, 34.4 mmol) and 4-dimethylaminopyridine (6.3 mg, 51.6 mmol) in 1.5 mL of dichloromethane at 0 °C was added triethylamine (57.6 μL, 0.413 mmol) and methanesulfonyl

chloride (16 μL, 0.206 mmol). After 30 min, 57.6 μL of triethylamine was added to the mixture which was filtered through a small pad of silica gel, and eluting with diethyl ether. The combined filtrates were concentrated and the residue was purified by chromatography on silica gel (50% ethyl acetate in hexanes as eluent) to give 7.1 mg (91%) of **180**: $[\alpha]_D^{23}$ +3.2° (*c* 0.71, $CHCl_3$); IR (neat) 2917, 1735, 1627, 1453, 1290, 1187, 1111, 943 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (3H, d, *J* = 7 Hz), 1.46 (3H, s), 2.96 (2H, s), 3.05-3.15 (1H, m), 3.82 (3H, s), 5.67 (1H, d, *J* = 2 Hz), 6.53 (1H, d, *J* = 2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 19.0, 33.2, 47.8, 53.4, 58.8, 84.4, 128.2, 137.1, 164.1, 171.3; LRMS *m/z* 227 [$(M + H)^+$, 20], 209 (20), 181 (60), 177 (20), 167 (60), 152 (30), 149 (20), 125 (100); HRMS calcd. for $C_{11}H_{15}O_5$ $(M + H)^+$ *m/z* 227.0920. Found: *m/z* 227.0919.

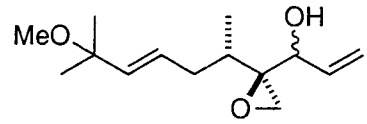


Dimethyl Ester 182. To a stirred solution of **180** (5.7 mg, 25.0 μmol) in methanol-water (1mL 1:1) at 0 °C was added 0.5 mL of 1M aqueous potassium hydroxide. After being stirred for 80 min, the reaction mixture was acidified to pH 3 with 3% aqueous phosphoric acid and was saturated with solid sodium chloride. The mixture was extracted with ethyl acetate (4 x 10 mL), and the combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was diluted with 5 mL of diethyl ether and an ethereal solution of diazomethane[95] was added until a yellow color persisted. The reaction mixture was stirred at room temperature for 1 h and was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (33% ethyl acetate in hexanes as eluent) to give 2.8 mg (37%) of **182**: $[\alpha]_D^{23}$

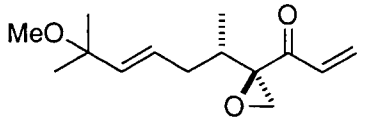
-44.1° (*c* 0.22, $CHCl_3$); IR (neat) 3477 (broad), 2939, 1733, 1635, 1448, 1365, 1151, 954 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (3H, d, *J* = 7 Hz), 1.48 (3H, s), 2.45 (1H, d, *J* = 5 Hz), 2.86 (1H, d, *J* = 5 Hz), 3.59 (2H, m), 3.76 (3H, s), 3.83 (3H, s), 5.54 (1H, s), 6.18 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.6, 21.9, 32.3, 45.1, 52.0, 52.8, 63.9, 75.2, 123.6, 140.7, 167.8, 174.4; LRMS *m/z* 259 [(M + H)$^+$, 30], 241 (20), 227 (30), 211 (10), 209 (100), 199 (50), 181 (30), 177 (50), 167 (40), 155 (30), 149 (20), 139 (20), 125 (60); HRMS calcd. for $C_{12}H_{19}O_6$ (M + H)$^+$ *m/z* 259.1182. Found: *m/z* 259.1181.



Spirodilactone 184. To a stirred solution of **182** (6.0 mg, 23..2 μmol) in tetrahydrofuran (2 mL) was added 1 mL of 3N aqueous sulfuric acid. The mixture was heated to reflux for 24 h and after cooling was extracted with chloroform (5 x 10 mL). The combined extracts were washed with brine (2 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5% ethanol in chloroform as eluent) to yield 2.1 mg (43%) of **184**: $[\alpha]_D^{25}$ +39.5° (*c* 0.21, EtOH); IR (neat) 3443 (broad), 2356, 1782, 1661, 1470, 1415, 1269, 1112, 1002 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (3H, d, *J* = 7 Hz), 1.60 (3H, s), 2.95 (1H, s), 3.08-3.15 (1H, m), 4.24 (2H, s), 5.71 (1H, d, *J* = 2 Hz), 6.30 (1H, d, *J* = 2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 19.6, 38.4, 73.1, 74.2, 88.5, 123.0, 139.8, 167.1, 176.1; LRMS m/z 213 [(M + H)$^+$, 100], 195 (50), 185 (20), 167 (20), 151 (20), 139 (10), 124 (30), 115 (80), 69 (10): HRMS calcd. for $C_{10}H_{13}O_5$ (M + H)$^+$ *m/z* 213.0763. Found: *m/z* 213.0764.

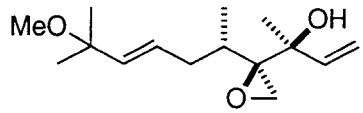


Alcohol 186. To a stirred solution of **162** (2.67 g, 12.6 mmol) in 50 mL of tetrahydrofuran at -78 °C was added vinyl magnesium bromide (18.9 mL, 1.0M, 18.9 mmol). The reaction mixture was stirred at -78 °C for 1 h and was quenched with 20 mL of water. The mixture was extracted with ethyl acetate (4 x 20 mL), and the combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (40% ethyl acetate in hexanes as eluent) to give 2.17 g (72%) of **186** as a mixture of two diastereomers: IR (neat) 3422 (broad), 2977, 2922, 2823, 2355, 1458, 1376, 1255, 1167, 1073, 985, 924 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (3H, dd, J = 7, 6 Hz), 1.25 (6H, d, J = 1 Hz), 1.67-1.77 (1H, m), 1.85-2.00 (2H, m), 2.23-2.33 (1H, m), 2.67 (1H, m), 2.86 (1H, m), 3.14 (3H, d, J = 1 Hz), 4.23-4.34 (1H, m), 5.20-5.56 (4H, m), 5.72-5.99 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 16.6, 25.7, 25.9, 33.4, 34.4, 34.5, 35.4, 47.0, 48.0, 50.2, 63.7, 70.7, 72.6, 74.7, 117.4, 118.4, 128.0, 128.3, 136.4, 137.1, 137.4; LRMS *m/z* 241 [$(M + H)^+$, 20], 197 (40), 181 (60), 163 (40), 151 (30), 139 (30), 135 (40), 125 (30), 123 (40), 121 (40), 113 (40), 109 (100), 97 (50), 95 (50), 85 (50), 83 (70), 81 (40), 73 (40), 71 (60), 69 (90), 67 (30); HRMS calcd. for $C_{14}H_{25}O_3$ $(M + H)^+$ *m/z* 241.1803. Found: *m/z* 241.1803.



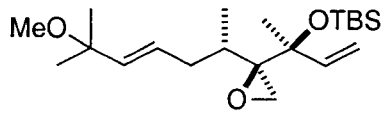
α,β-Unsaturated Ketone 187. To a stirred solution of **186** (2.00 g, 8.33 mmol) in water (300 μL, 16.7 mmol) and dichloromethane (50 mL) was added Dess-Martin's periodinane (7.06 g, 16.7 mmol). After being stirred for 1

h, the reaction mixture was diluted with 50 mL of diethyl ether and was filtered through a small pad of silica gel, eluting with diethyl ether (4 x 50 mL). The combined filtrates were concentrated and the residue was purified by chromatography on silica gel (14% ethyl acetate in hexanes as eluent) to provide 1.98 g (100%) of **187**: $[\alpha]_D^{23}$ +22.1° (*c* 1.65, $CHCl_3$); IR (neat) 2975, 2934, 2821, 1696, 1607, 1465, 1406, 1257, 1157, 1074, 985, 855, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (3H, d, *J* = 7 Hz), 1.22 (6H, s), 2.02-2.12 (1H, m), 2.24-2.33 (1H, m), 2.37-2.48 (1H, m), 2.80 (1H, d, *J* = 5 Hz), 2.97 (1H, d, *J* = 5 Hz), 3.12 (3H, s), 5.40-5.55 (2H, m), 5.74 (1H, dd, *J* = 10, 2 Hz), 6.43 (1H, dd, *J* = 17, 2 Hz), 6.63 (1H, dd, *J* = 17, 10 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.7, 25.6, 25.9, 33.1, 36.0, 49.1, 50.2, 64.7, 74.7, 128.0, 129.1, 130.5, 137.3, 198.0; LRMS *m/z* 239 $(M + H)^+$, 237 (60), 223 (30), 207 (60), 191 (20), 189 (60), 175 (20), 161 (20), 151 (20), 135 (40), 125 (20), 123 (40), 113 (40), 109 (100), 107 (20), 91 (20), 81 (20), 76 (20); HRMS calcd. for $C_{14}H_{21}O_3$ $(M - H)^+$ *m/z* 237.1491, $C_{13}H_{19}O_3$ $(M - CH_3)^+$ *m/z* 223.1334. Found: *m/z* 237.1491, 223.1334.



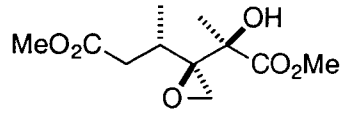
Alcohol 189. To a stirred solution of **187** (760 mg, 3.19 mmol) in 10 mL of tetrahydrofuran at -78 °C was added dropwise a pre-cooled solution (-78 °C) of methylmagnesium bromide (1.60 mL, 3.0M, 4.79 mmol) in 27 mL of tetrahydrofuran during 20 min. After addition was completed, the reaction mixture was immediately quenched with 10 mL of saturated aqueous ammonium chloride and was allowed to warm to room temperature. The mixture was diluted with 10 mL of water, the organic layer was separated, and

the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo.* The residue was purified by chromatography on silica gel (14% ethyl acetate in hexanes followed by 25% ethyl acetate in hexane as eluent) to afford 489 mg (60%) of **189** as a single diastereomer along with 253.7 mg (33%) of recovered **187**. **189**: $[\alpha]_D^{23}$ +12.9° (*c* 6.65, $CHCl_3$); IR (neat) 3444 (broad), 2980, 2931, 2825, 1465, 1379, 1163, 996, 921, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, d, *J* = 7 Hz), 1.25 (6H, s), 1.38 (3H, s), 1.60-170 (1H, m), 2.02-2.19 (2H, m), 2.31 (1H, s), 2.59 (1H, d, *J* = 5 Hz), 2.99 (1H, d, *J* = 5 Hz), 3.14 (3H, s), 5.20 (1H, dd, *J* = 11, 1 Hz), 5.36 (1H, dd, *J* = 17, 1 Hz), 5.39-5.53 (2H, m), 5.92 (1H, dd, *J* = 17, 11 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 23.4, 25.7, 25.8, 31.9, 35.2, 46.7, 50.1, 66.6, 72.8, 74.6, 114.8, 128.8, 136.8, 140.4; LRMS *m/z* 239 (20), 237 (20), 223 (90), 209 (40), 205 (80), 193 (30), 109 (100); HRMS calcd. for $C_{14}H_{23}O_3$ $(M - CH_3)^+$ *m/z* 239.1647, $C_{15}H_{25}O_2$ $(M - OH)^+$ *m/z* 237.1855. Found: *m/z* 239.1648, 237.1854.



Siloxy Ether 190. To a stirred solution of **189** (238.0 mg, 0.936 mmol) in 6 mL of dichloromethane was added 2,6-lutidine (327 μL, 2.81 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (322.4 μL, 1.40 mmol) at -78 °C. The reaction mixture was allowed to stir for 2 h at -78 °C and for 22 h at 4 °C, then was quenched with 10 mL of saturated aqueous sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic extracts were washed with brine,

dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (5% ethyl acetate in hexanes as eluent) to give 231 mg (67%) of **190**: $[\alpha]_D^{23}$ -1.1° (*c* 5.02, $CHCl_3$); IR (neat) 2963, 2942, 2896, 2865, 2814, 1468, 1412, 1381, 1252, 1083, 1052, 985, 944, 847, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.06 (6H, s), 0.88 (9H, s), 0.90 (3H, d, *J* = 8 Hz), 1.23 (6H, s), 1.34 (3H, s), 1.55-1.65 (1H, m), 2.11-2.25 (2H, m), 2.49 (1H, d, *J* = 5 Hz), 2.75 (1H, d, *J* = 5 Hz), 3.12 (3H, s), 5.12 (1H, dd, *J* = 11, 1 Hz), 5.21 (1H, dd, *J* = 18, 1 Hz), 5.35-5.56 (2H, m), 5.93 (1H, dd, *J* = 18, 11 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -2.2, -2.1, 18.4, 19.5, 22.4, 25.82, 25.85, 25.92, 31.0, 35.6, 46.3, 50.2, 66.6, 74.7, 114.2, 129.3, 136.4, 142.1; LRMS m/z 369 $(M + H)^+$, 353 (10), 337 (100), 321 (20), 307 (60), 279 (30), 239 (20), 225 (40), 205 (30), 187 (20), 185 (60); HRMS calcd. for $C_{21}H_{41}O_3Si$ $(M + H)^+$ *m/z* 369.2825, $C_{20}H_{37}Si$ $(M - CH_3)^+$ *m/z* 353.2512. Found: *m/z* 369.2825, 353.2511.

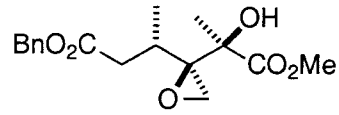


Dimethyl Ester 192. Ozone was passed through a stirred suspension of **190** (350 mg, 0.950 mmol) and sodium bicarbonate (80 mg, 0.950 mmol) in 10 mL of dichloromethane and 2 mL of methanol at -78 °C until a blue color persisted. The reaction mixture was stirred at -78 °C for 20 min and was allowed to warm to room temperature while a stream of argon was passed through the solution until it was clear and colorless. To the mixture was added triethylamine (795 μL, 5.70 mmol) and acetic anhydride (538 μL, 5.70 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was filtered and concentrated *in vacuo*, and the residue was passed through a short

column of silica gel (14% ethyl acetate in hexanes as eluent). The solvent was removed, and the residue was taken up in 2-methyl-2-butene (4.0 mL) and 15 mL of *tert*-butanol. To this solution at 0 °C was added dropwise a solution of sodium chlorite (787 mg, 8.70 mmol) and sodium phosphate monobasic, monohydrate (744 mg) in 6 mL of water. The reaction mixture was stirred at room temperature for 1.5 h and the organic layer was separated. The aqueous layer was washed once with hexane (10 mL) and was kept for further treatment. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was diluted with diethyl ether and an ethereal solution of diazomethane[95] was added until a yellow color persisted. The reaction mixture was stirred at room temperature overnight, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (50% ethyl acetate in hexanes as eluent) to give 113.9 mg of **192**.

The aqueous layer obtained above was acidified to pH 3 with 3% aqueous phosphoric acid and was extracted with ethyl acetate (5 x 10 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was diluted with diethyl ether and an ethereal solution of diazomethane[95] was added until a yellow color persisted. The reaction mixture was stirred overnight, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give an additional 38.4 mg (total 152.3 mg, 65%) of **192**: $[\alpha]_D^{23}$ -3.2° (*c* 3.39, $CHCl_3$); IR (neat) 3488 (broad), 2993, 2960, 1750, 1447, 1381, 1266, 1227, 1161, 1106, 1013, 935, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (3H, d, *J* = 7 Hz), 1.44 (3H, s), 1.98-2.23 (2H, m), 2.60 (1H, d, *J* = 4 Hz), 2.77-2.89 (1H, m), 2.98 (1H, d, *J* = 4 Hz), 3.67 (3H, s), 3.72 (1H, s), 3.81 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 21.9, 28.5, 36.6, 46.1, 51.6, 52.9, 63.6, 77.0, 173.2, 174.4; LRMS *m/z* 247

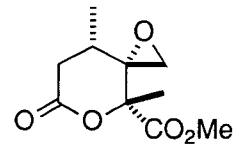
[$(M + H)^+$, 20], 215 (30), 197 (100), 187 (30), 185 (20), 169 (40), 165 (90), 155 (90), 143 (20), 141 (20), 137 (20), 127 (30), 113 (80), 85 (20), 69 (20); HRMS calcd. for $C_{11}H_{19}O_6$ $(M + H)^+$ *m/z* 247.1182. Found: *m/z* 247.1182.



Benzyl Methyl Ester 202. To a stirred suspension of **190** (139 mg, 0.377 mmol) and sodium bicarbonate (31.7 mg, 0.377 mmol) in 5 mL of dichloromethane at room temperature was added benzyl alcohol (390 μL, 3.77 mmol). The reaction mixture was stirred at -78 °C and ozone was passed through the mixture for 5 min. The reaction mixture was stirred for an additional 10 min and was allowed to warm to room temperature while a stream of argon was passed through the solution until it was clear and colorless. To the reaction mixture was added triethylamine (525 μL, 3.77 mmol) and acetic anhydride (356 μL, 3.77 mmol), and the solution was stirred at room temperature for 30 min, filtered, and concentrated *in vacuo*. The residue was passed through a short column of silica gel (33% of ethyl acetate in hexanes as eluent) to remove the residual benzyl alcohol.

To a stirred solution of the crude aldehyde and 2-methyl-2-butene (1.6 mL) in 10 mL of *tert*-butanol at room temperature was added dropwise a solution of sodium chlorite (313.7 mg, 3.47 mmol) and sodium phosphate monobasic, monohydrate (313.7 mg) in 5 mL of water. The reaction mixture was stirred at room temperature for 3 h and the organic layer was separated. The aqueous layer was acidified to pH 3 with 3% aqueous phosphoric acid and was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and

concentrated *in vacuo*. The residue was diluted with 5 mL of diethyl ether and an ethereal solution of diazomethane was added until a yellow color persisted. The solution was stirred overnight and was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica ge (50% ethyl acetate in hexanes as eluent) to give 57 mg (47%) of **202**: $[\alpha]_D^{23}$ +1.37° (*c* 1.82, $CHCl_3$); IR (neat) 3492 (broad), 2950, 1732, 1493, 1453, 1384, 1350, 1260, 1214, 1159, 1103, 984, 928, 751, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (3H, d, *J* = 7 Hz), 1.43 (3H, s), 2.07 (1H, dd, *J* = 17, 6 Hz), 2.25 (1H, dd, *J* = 17, 9 Hz), 2.60 (1H, d, *J* = 4 Hz), 2.80-2.93 (1H, m), 2.98 (1H, d, *J* = 4 Hz), 3.70 (1H, s, broad), 3.78 (3H, s), 5.12 (2H, d, *J* = 3 Hz), 7.32-7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 21.9, 28.6, 36.9, 46.1, 52.9, 63.6, 66.3, 128.2, 128.3, 128.5, 136.0, 172.6, 174.4; LRMS *m/z* 323 $[(M + H)^+$, 50], 305 (40), 275 (20), 263 (20), 215 (80), 197 (50), 185 (40), 181 (20), 169 (40), 165 (20), 155 (100), 139 (40), 129 (30), 119 (60), 113 (70), 107 (20), 91 (100); HRMS calcd. for $C_{17}H_{23}O_6$ $(M + H)^+$ *m/z* 323.1495. Found: *m/z* 323.1495.



δ-Lactone 204. A mixture of **202** (41.6 mg, 0.129 mmol) and 10% palladium on activated carbon (20 mg) in 3 mL of methanol was stirred under an hydrogen atmosphere at room temperature for 20 h. The mixture was diluted with ethyl acetate, filtered through a small pad of Celite, and concentracted *in vacuo* to yield crude **203**.

To a stirred mixture of 2-chloro-1-methylpyridinium iodide (98.9 mg, 0.387 mmol) and 4-dimethylaminopyridine (78.9 mg 0.646 mmol) in 2 mL of

acetonitrile was added the crude **203** obtained above in 2 mL of acetonitrile via cannula. An additional 2 mL of acetonitrile was used to ensure that all of the alcohol was transferred to the reaction flask. After stirring for 24 h at room temperature, 5 mL of diethyl ether was added to the solution which was filtered through a small pad of silica gel, eluting with diethyl ether. The eluent was concentrated and the residue was purified by chromatography on silica gel (55% ethyl acetate in hexanes as eluent) to give 27.3 mg (99%) of **204**: $[\alpha]_D^{23}$ +52.8° (*c* 2.32, $CHCl_3$); IR (neat) 2949, 1744, 1453, 1442, 1381, 1260, 1194, 1117, 1002, 947 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (3H, d J = 6 Hz), 1.71 (3H, s), 2.43-2.70 (3H, m), 2.99 (2H, dd, J = 6, 4 Hz), 3.75 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2, 23.1, 26.3, 35.6, 48.3, 53.0, 59.9, 85.8, 168.7, 169.4; LRMS *m/z* 215 [$(M + H)^+$, 30], 197 (30), 185 (20), 169 (70), 165 (30), 155 (100), 153 (20), 127 (30), 113 (70), 69 (20); HRMS calcd. for $C_{10}H_{15}O_5$ $(M + H)^+$ *m/z* 215.0920. Found: *m/z* 215.0919.

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APPENDICES

APPENDIX A
SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON (+)-NEMORENSINE (1)

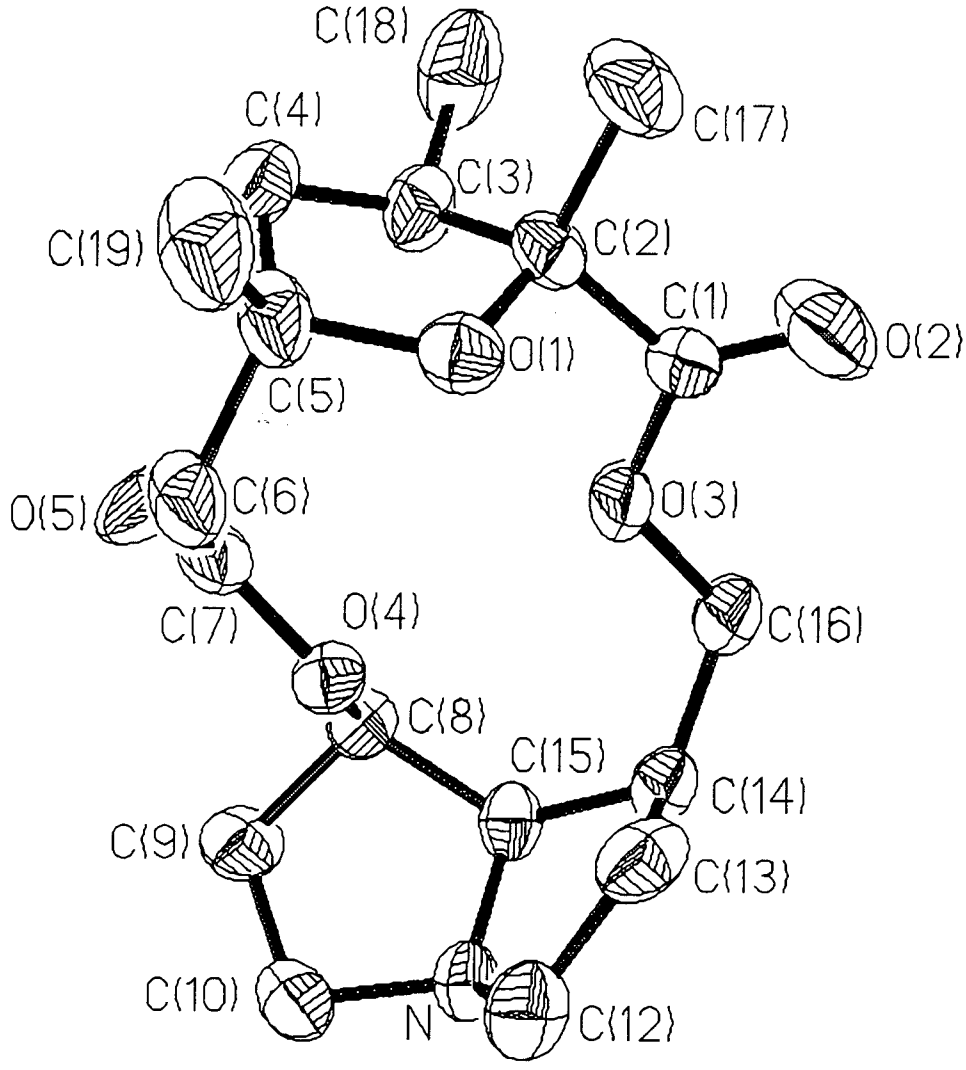

Table 1. Crystal Data and Structure Refinement for Nemorensine (1)

Empirical Formula	$C_{18}H_{27}NO_5$	
Formula Weight	337.4	
Temperature	296 (2) K	
Wavelength	1.54178 Å	
Crystal Color, Habit	Yellow, plate	
Crystal System	Orthorhombic	
Space Group	P2(1)2(1)2(1)	
Unit Cell Dimensions:	a = 6.721(1) Å	$\alpha = 90°$
	b = 10.819(2) Å	$\beta = 90°$
	c = 25.003(5) Å	$\gamma = 90°$
Volume	1818.65 $Å^3$	
Z	4	
Density (calculated)	1.233 Mg/m^3	
F(000)	728.00	
Crystal Size	0.01 x 0.070 x 0.050 mm^3	
Diffractometer	Simens P4	
Reflections Collected	2002	
Independent Reflections	1823 [R(int) = 0.0442]	
No. Observations [I <4.00sig(I)]	1641	
No. Variables	217	
Reflection/Parameter Ratio	7.6:1	
Residuals: R; Rw	0.0549; 0.0680	
Goodness- of-Fit on F^2	1.41	
Max Shift/Error in Final Cycle	0.00	
Largest Diff. Peak and Hole	0.27 and -0.22 $e.Å^{-3}$	

Table 2. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Nemorensine (1)

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N	-20(8)	-7023(5)	-4568(2)	39(2)
O(1)	-1406(7)	-2782(4)	-3202(2)	42(2)
O(2)	-1798(13)	-1407(4)	-4398(2)	91(3)
O(3)	-2058(10)	-3376(4)	-4239(2)	66(2)
O(4)	-1912(7)	-5630(4)	-3690(2)	36(1)
O(5)	-4818(10)	-5724(5)	-3239(2)	69(2)
C(1)	-2143(11)	-2212(6)	-4099(3)	40(2)
C(2)	-2754(10)	-2061(5)	-3513(3)	37(2)
C(3)	-4834(10)	-2632(7)	-3411(3)	45(2)
C(4)	-4637(12)	-3018(7)	-2823(3)	53(3)
C(5)	-2431(13)	-3392(6)	-2763(3)	48(3)
C(6)	-1962(15)	-4791(6)	-2816(3)	54(3)
C(7)	-3103(15)	-5430(6)	-3258(3)	51(3)
C(8)	-2895(11)	-6181(5)	-4148(3)	37(2)
C(9)	-2975(12)	-7589(6)	-4078(3)	49(2)
C(10)	-831(11)	-7988(7)	-4213(3)	52(3)
C(12)	1825(11)	-6412(6)	-4376(3)	54(3)
C(13)	1482(11)	-5008(7)	-4424(3)	54(3)
C(14)	-375(11)	-4908(6)	-4779(3)	43(2)
C(15)	-1560(10)	-6073(6)	-4645(2)	37(2)
C(16)	-1457(14)	-3686(6)	-4783(3)	58(3)
C(17)	-2567(14)	-697(6)	-3349(3)	64(3)
C18)	-6619(12)	-1826(8)	-3544(3)	75(3)
C(19)	-1503(15)	-2937(7)	-2236(3)	73(3)

Table 3. Bond Lengths [Å] for Nemorensine (1)

Atom 1	Atom 2	Distance	Atom 1	Atom2	Distance
O(1)	C(5)	1.455(8)	N	C(15)	1.471(9)
O(1)	C(2)	1.427(8)	N	C(12)	1.486(9)
O(4)	C(7)	1.360(9)	N	C(10)	1.475(9)
O(4)	C(8)	1.450(7)	C(5)	C(19)	1.537(10)
O(3)	C(1)	1.309(8)	C(3)	C(18)	1.520(11)
C(4)	C(5)	1.544(11)	O(3)	C(16)	1.458(8)
C(4)	C(3)	1.534(10)	C(14)	C(15)	1.528(9)
O(5)	C(7)	1.197(12)	C(14)	C(16)	1.508(10)
O(2)	C(1)	1.171(8)	C(14)	C(13)	1.536(10)
C(2)	C(1)	1.529(9)	C(15)	C(8)	1.538(9)
C(6)	C(5)	1.551(9)	C(12)	C(13)	1.540(10)
C(8)	C(9)	1.535(8)	C(17)	C(2)	1.538(9)
C(3)	C(2)	1.550(10)	C(10)	C(9)	1.541(11)
C(7)	C(6)	1.513(11)			

Table 4. Bond Angles [°] for Nemorensine (1)

Atoms (1-2-3)	Angle	Atoms (1-2-3)	Angle
C(5)-O(1)-C(2)	111.1(5)	N-C(12)-C(13)	106.8(6)
C(7)-O(4)-C(8)	115.1(6)	N-C(15)-C(8)	104.6(5)
O(4)-C(7)-O(5)	123.8(7)	N-C(10)-C(9)	106.2(5)
O(4)-C(7)-C(6)	110.7(8)	C(17)-C(2)-C(1)	109.6(5)
O(5)-C(7)-C(6)	125.4(7)	C(16)-O(3)-C(1)	118.9(5)
C(5)-C(4)-C(3)	104.3(6)	C(8)-C(9)-C(10)	102.7(6)
C(7)-C(6)-C(5)	113.9(6)	O(4)-C(8)-C(15)	110.0(5)
O(4)-C(8)-C(9)	109.5(5)	C(15)-C(8)-C(9)	100.8(5)
O(1)-C(5)-C(4)	105.2(5)	O(1)-C(5)-C(19)	107.9(6)
O(1)-C(5)-C(6)	106.4(5)	C(4)-C(5)-C(19)	112.9(6)
C(4)-C(5)-C(6)	116.3(7)	C(6)-C(5)-C(19)	107.7(6)
C(4)-C(3)-C(2)	100.9(5)	C(4)-C(3)-C(18)	115.7(6)
O(1)-C(2)-C(3)	105.4(5)	C(2)-C(3)-C(18)	116.6(6)
O(1)-C(2)-C(1)	107.1(5)	O(1)-C(2)-C(17)	109.1(5)
C(3)-C(2)-C(1)	111.0(5)	C(3)-C(2)-C(17)	114.4(6)
O(3)-C(1)-O(2)	122.4(6)	C(14)-C(15)-C(8)	122.9(5)
O(3)-C(1)-C(2)	111.8(5)	O(3)-C(16)-C(14)	109.2(5)
O(2)-C(1)-C(2)	125.8(6)	C(14)-C(13)-C(12)	103.7(6)
C(15)-N-C(12)	108.6(5)	C(15)-C(14)-C(16)	118.2(6)
C(15)-N-C(10)	108.2(5)	C(15)-C(14)-C(13)	103.8(5)
C(12)-N-C(10)	115.4(5)	C(16)-C(14)-C(13)	117.2(6)
N-C(15)-C(14)	103.8(5)		

Table 5. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Nemorensine (1)

The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [h^2a^{*2}U11 + ... + 2 h K a^* b^* U12]$

Atom	U11	U22	U33	U12	U13	U23
O(1)	40(3)	42(3)	44(3)	0(3)	-4(2)	5(2)
O(2)	181(7)	41(3)	52(3)	1(5)	15(5)	12(3)
O(3)	115(5)	33(3)	52(3)	3(3)	47(4)	2(2)
O(4)	44(3)	35(2)	29(2)	-7(3)	1(2)	-2(2)
O(5)	76(4)	62(4)	71(4)	-34(4)	38(4)	-17(3)
N	38(3)	41(3)	40(3)	4(3)	1(3)	-8(3)
C(1)	40(4)	34(4)	45(4)	1(4)	4(4)	4(3)
C(2)	41(4)	27(3)	45(4)	-1(4)	-1(4)	-7(3)
C(3)	36(4)	50(4)	48(4)	2(4)	8(4)	-11(4)
C(4)	56(5)	53(5)	49(4)	-4(5)	18(4)	-10(4)
C(5)	73(6)	41(4)	31(4)	2(4)	-4(4)	-9(3)
C(6)	93(6)	42(4)	28(3)	3(5)	-3(4)	2(3)
C(7)	87(6)	25(4)	41(4)	-5(5)	10(5)	3(3)
C(8)	37(4)	35(3)	39(4)	-6(4)	4(4)	-6(3)
C(9)	57(5)	35(4)	54(4)	-13(4)	1(4)	-5(3)
C(10)	57(5)	42(4)	57(5)	10(4)	0(4)	3(4)
C(12)	39(4)	60(5)	61(5)	2(4)	-2(4)	-16(4)
C(13)	45(4)	55(5)	60(5)	-16(4)	13(4)	-10(4)
C(14)	51(5)	43(4)	34(4)	2(4)	12(4)	0(3)
C(15)	42(4)	42(4)	29(3)	3(4)	-2(3)	-6(3)
C(16)	87(6)	45(4)	42(4)	3(5)	29(5)	4(3)
C(17)	84(7)	34(4)	72(5)	-4(5)	-2(5)	-11(4)
C(18)	46(5)	106(7)	73(5)	24(6)	5(5)	-9(6)
C(19)	108(8)	66(5)	44(4)	7(6)	-14(5)	-17(4)

Table 6. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^2 x 10^3) for Nemorensine (1)

	x	y	z	U(eq)
H(3A)	4934	3372	3621	80
H(4A)	5500	3697	2737	80
H(4B)	4942	2335	2592	80
H(6A)	2265	5190	2483	80
H(6B)	564	4891	2882	80
H(8A)	4198	5843	4206	80
H(9A)	3288	7800	3715	80
H(9B)	3919	7981	4311	80
H(10A)	832	8776	4389	80
H(10B)	37	8049	3895	80
H(12A)	-2072	6637	4011	80
H(12B)	-2946	6656	4589	80
H(13A)	-2603	4600	4583	80
H(13B)	-1225	4646	4080	80
H(14A)	-114	5032	5135	80
H(15A)	2318	6295	4956	80
H(16A)	2609	3747	5008	80
H(16B)	608	3047	4920	80
H(17A)	1246	397	3417	80
H(17B)	2860	620	2975	80
H(17C)	3506	220	3552	80
H(18A)	7827	2270	3471	80
H(18B)	6581	1597	3914	80
H(18C)	6572	1096	3326	80
H(19A)	1771	2071	2193	80
H(19B)	91	3068	2247	80
H(19C)	2063	3386	1942	80

Table 7. Torsion Angles [°] for Nemorensine (1)

Atoms (1-2-3-4)	Angle	Atoms (1-2-3-4)	Angle
N-C(15)-C(8)-O(4)	-75.8	C(7)-C(6)-C(5)-C(19)	-168.9
N-C(15)-C(8)-C(9)	39.8	C(5)-C(4)-C(3)-C(18)	160.4
N-C(10)-C(9)-C(8)	25.5	C(12)-N-C(15)-C(14)	-28.7
C(15)-N-C(10)-C(9)	-0.6	C(16)-C(14)-C(15)-N	168.8
C(12)-N-C(10)-C(9)	-122.5	C(13)-C(14)-C(15)-N	36.9
C(5)-C(4)-C(3)-C(2)	33.6	C(10)-N-C(15)-C(14)	-154.6
C(8)-O(4)-C(7)-O(5)	-3.0	C(15)-N-C(12)-C(13)	9.1
C(8)-O(4)-C(7)-C(6)	176.8	C(10)-N-C(12)-C(13)	130.8
C(12)-N-C(15)-C(8)	101.2	C(7)-O(4)-C(8)-C(15)	-166.4
O(4)-C(7)-C(6)-C(5)	-103.5	C(5)-O(1)-C(2)-C(17)	-100.2
O(5)-C(7)-C(6)-C(5)	76.4	C(18)-C(3)-C(2)-C(1)	83.4
C(7)-O(4)-C(8)-C(9)	83.7	C(16)-O(3)-C(1)-O(2)	-1.8
C(10)-N-C(15)-C(8)	-24.7	C(16)-O(3)-C(1)-C(2)	178.8
C(2)-O(1)-C(5)-C(4)	-1.2	C(4)-C(3)-C(2)-C(17)	84.9
C(2)-O(1)-C(5)-C(6)	-125.0	N-C(12)-C(13)-C(14)	14.1
O(1)-C(2)-C(1)-O(3)	-54.4	O(4)-C(8)-C(9)-C(10)	76.7
O(1)-C(2)-C(1)-O(2)	126.2	C(17)-C(2)-C(1)-O(3)	-172.7
C(3)-C(2)-C(1)-O(3)	60.0	C(17)-C(2)-C(1)-O(2)	8.0
C(3)-C(2)-C(1)-O(2)	-119.3	C(15)-C(8)-C(9)-C(10)	-39.3
C(3)-C(4)-C(5)-O(1)	-21.3	C(14)-C(15)-C(8)-O(4)	41.7
C(3)-C(4)-C(5)-C(6)	96.0	C(14)-C(15)-C(8)-C(9)	157.2
C(7)-C(6)-C(5)-O(1)	75.6	C(1)-O(3)-C(16)-C(14)	-148.3
C(7)-C(6)-C(5)-C(4)	-41.1	C(18)-C(3)-C(2)-C(17)	-41.2
C(5)-O(1)-C(2)-C(3)	23.0	C(16)-C(14)-C(15)-C(8)	50.9
C(5)-O(1)-C(2)-C(1)	141.3	C(13)-C(14)-C(15)-C(8)	-80.9
C(4)-C(3)-C(2)-O(1)	-34.9	C(15)-C(14)-C(16)-O(3)	-67.8
C(4)-C(3)-C(2)-C(1)	-150.4	C(13)-C(14)-C(16)-O(3)	57.7
C(18)-C(3)-C(2)-O(1)	-161.0	C(15)-C(14)-C(13)-C(12)	-31.0
C(2)-O(1)-C(5)-C(19)	119.6	C(16)-C(14)-C(13)-C(12)	-163.4
C(3)-C(4)-C(5)-C(19)	-138.8		

APPENDIX B
SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON α-METHYLENE LACTONE 180

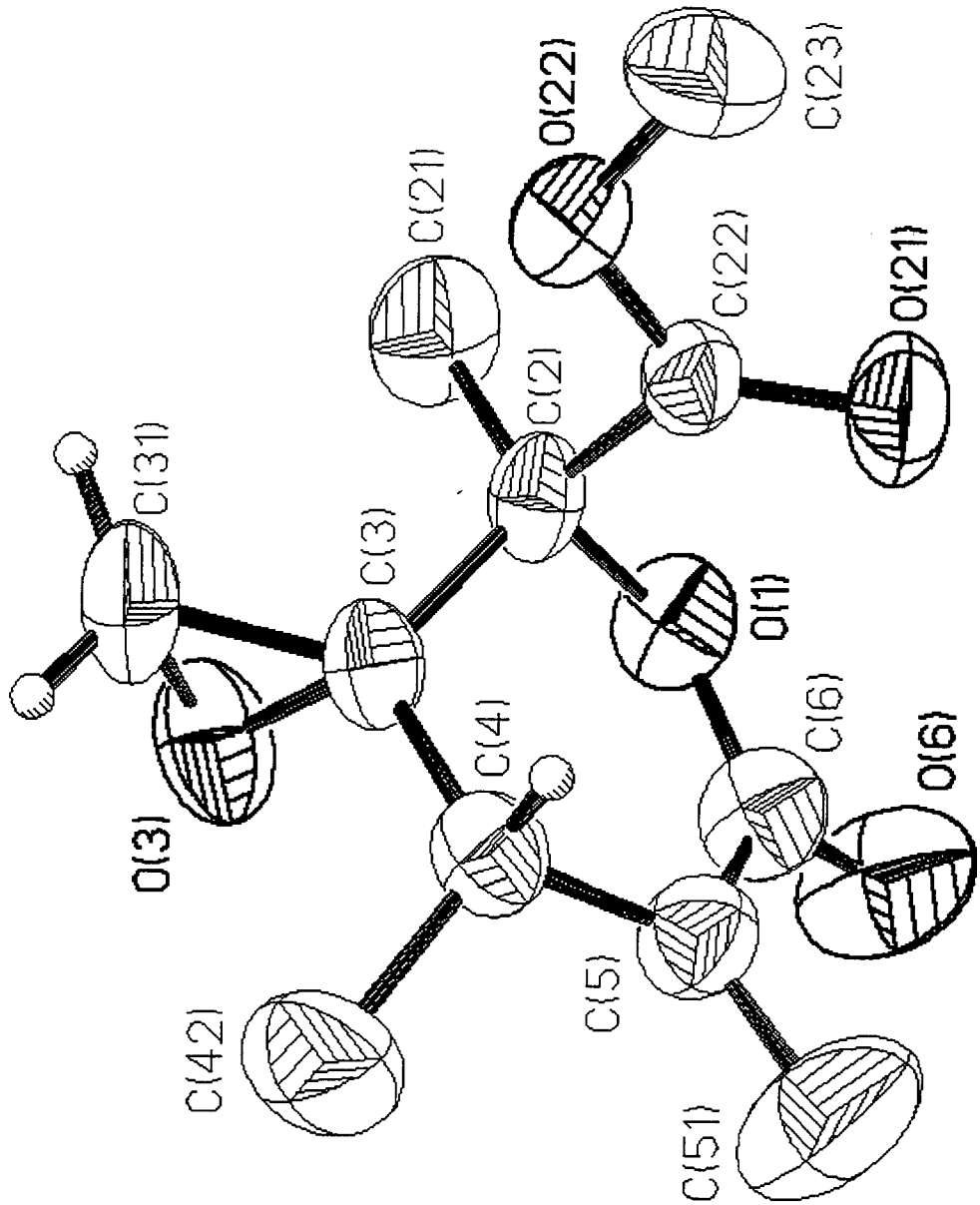

Table 1. Crystal Data and Structure Refinement for α-Methylene Lactone 180

Identification code	STR3	
Empirical formula	$C_{11}H_{14}O_5$	
Formula weight	226.22	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.464(1) Å	α = 90°
	b = 12.331(1) Å	β = 90°
	c = 14.434(1) Å	γ = 90°
Volume	1150.43(14) $Å^3$	
Z	4	
Density (calculated)	1.306 Mg/m^3	
Absorption coefficient	0.876 mm^{-1}	
F(000)	480	
Crystal size	0.3 x 0.3 x 0.02 mm^3	
Theta range for data collection	4.72 to 57.08 °	
Index ranges	-7<=h<=4, -13<=k<=9, -15<=1<=10	
Reflections collected / unique	1436 / 1236 [R(int) = 0.0482]	
Completeness to 2theta = 57.08	98.1%	
Absorption correction	Empirical (psi-scans)	
Max. and min. transmission	0.998 and 0.616	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1236 / 0 / 164	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0411, wR2 = 0.1140	
R indices (all data)	R1 = 0.0437, wR2 = 0.1181	
Absolute structure parameter	0.0(4)	
Extinction coefficient	0.019(2)	
Largest diff. peak and hole	0.134 and -0.151 $e.Å^{-3}$	

Table 2. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for α-Methylene Lactone 180

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	6778(3)	2133(2)	7548(2)	74(1)
C(2)	6982(4)	3188(2)	7114(2)	59(1)
C(21)	4874(5)	3418(4)	6692(3)	94(1)
C(22)	8626(5)	3086(2)	6364(2)	54(1)
O(21)	9662(4)	2311(2)	6229(2)	88(1)
O(22)	8734(4)	3989(2)	5883(1)	74(1)
C(23)	10315(8)	4042(3)	5159(2)	90(1)
C(3)	7693(4)	3984(2)	7851(2)	58(1)
O(3)	6096(4)	4257(2)	8501(2)	94(1)
C(31)	6864(7)	5081(3)	7876(4)	87(1)
C(4)	9765(5)	3703(2)	8258(2)	60(1)
C(42)	10357(8)	4381(3)	9096(3)	107(1)
C(5)	9868(5)	2495(3)	8462(2)	69(1)
C(51)	11440(9)	2050(4)	8877(4)	137(2)
C(6)	8221(6)	1761(3)	8130(3)	77(1)
O(6)	8026(6)	830(2)	8380(3)	129(1)

Table 3. Bond Lengths [Å] for α-Methylene Lactone 180

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O(1)	C(6)	1.336(4)	O(3)	C(31)	1.446(5)
O(1)	C(2)	1.450(4)	C(4)	C(42)	1.519(5)
C(2)	C(3)	1.517(4)	C(5)	C(51)	1.301(6)
C(3)	O(3)	1.435(4)	C(2)	C(21)	1.519(5)
C(3)	C(4)	1.504(4)	C(2)	C(22)	1.523(4)
C(4)	C(5)	1.520(4)	C(22)	O(21)	1.182(3)
C(5)	C(6)	1.477(5)	C(22)	O(22)	1.314(3)
C(6)	O(6)	1.210(4)	O(22)	C(23)	1.463(5)
C(3)	C(31)	1.455(5)			

Table 4. Bond Angles [°] for α-Methylene Lactone 180

Atoms (1-2-3)	Angle	Atoms (1-2-3)	Angle
C(6)-O(1)-C(2)	121.0(2)	O(3)-C(3)-C(31)	60.0(2)
O(1)-C(2)-C(3)	107.8(3)	C(3)-O(3)-C(31)	60.7(2)
O(3)-C(3)-C(4)	116.1(3)	O(3)-C(31)-C(3)	59.3(2)
O(3)-C(3)-C(2)	113.1(2)	C(31)-C(3)-C(4)	122.2(3)
C(4)-C(3)-C(2)	113.2(2)	C(31)-C(3)-C(2)	120.5(3)
C(3)-C(4)-C(5)	109.9(3)	C(3)-C(4)-C(42)	114.1(3)
C(6)-C(5)-C(4)	120.4(3)	C(42)-C(4)-C(5)	112.0(3)
O(6)-C(6)-O(1)	116.1(3)	C(51)-C(5)-C(6)	117.0(3)
O(6)-C(6)-C(5)	124.0(4)	C(51)-C(5)-C(4)	122.4(3)
O(1)-C(6)-C(5)	119.8(3)	C(21)-C(2)-C(22)	110.8(3)
O(1)-C(2)-C(21)	105.0(2)	O(22)-C(22)-C(2)	110.0(2)
C(3)-C(2)-C(21)	115.6(3)	O(21)-C(22)-C(2)	125.4(3)
O(1)-C(2)-C(22)	107.2(2)	O(21)-C(22)-O(22)	124.6(3)
C(3)-C(2)-C(22)	109.9(2)	C(22)-O(22)-C(23)	116.9(3)

Table 5. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for α-Methylene Lactone 180

The anisotropic displacement factor exponent takes the form:
$-2\pi^2[h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

Atom	U11	U22	U33	U23	U13	U12
O(1)	65(1)	60(1)	96(2)	4(1)	-1(1)	-19(1)
C(2)	49(2)	46(2)	82(2)	-6(1)	0(1)	-1(1)
C(21)	53(2)	104(3)	125(3)	-13(2)	-17(2)	6(2)
C(22)	59(2)	45(1)	59(2)	-7(1)	-9(1)	4(2)
O(21)	113(2)	57(1)	93(2)	1(1)	22(2)	31(1)
O(22)	92(2)	57(1)	72(1)	8(1)	-1(1)	11(1)
C(23)	122(3)	93(3)	55(2)	11(2)	11(2)	5(2)
C(3)	52(2)	52(2)	69(2)	-8(1)	10(1)	0(1)
O(3)	88(2)	92(2)	101(2)	-20(2)	41(1)	5(1)
C(31)	92(3)	59(2)	109(3)	-20(2)	8(3)	21(2)
C(4)	64(2)	52(2)	65(2)	-4(1)	1(2)	-9(2)
C(42)	139(4)	83(3)	100(3)	-16(2)	-36(3)	-21(3)
C(5)	74(2)	60(2)	75(2)	4(2)	-6(2)	1(2)
C(51)	141(4)	78(3)	190(6)	20(3)	-82(5)	-3(3)
C(6)	83(2)	58(2)	90(2)	10(2)	2(2)	-16(2)
O(6)	160(3)	69(2)	160(3)	44(2)	-40(2)	-43(2)

Table 6. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for α-Methylene Lactone 180

Atom	x	y	z	U(eq)
H(21A)	4460(2)	2824(18)	6337(18)	126(5)
H(21B)	4957(11)	4030(2)	6316(19)	126(5)
H(21C)	3910(3)	3540(2)	7164(12)	126(5)
H(23A)	10160(15)	4730(6)	4810(7)	126(5)
H(23B)	10140(15)	3420(7)	4730(6)	126(5)
H(23C)	11720(4)	4010(12)	5448(10)	126(5)
H(23D)	11190(15)	3370(6)	5180(7)	126(5)
H(23E)	11210(15)	4690(7)	5260(6)	126(5)
H(23F)	9632(18)	4100(12)	4540(18)	126(5)
H(31A)	7710(6)	5610(3)	8210(3)	87(11)
H(31B)	6030(8)	5370(4)	7420(3)	116(16)
H(4)	10810(5)	3851(8)	7770(2)	126(5)
H(42A)	10340(4)	5150(2)	8928(8)	126(5)
H(42B)	11750(4)	4178(16)	9303(13)	126(5)
H(42C)	9360(4)	4250(18)	9599(15)	126(5)
H(51A)	11495(10)	1240(3)	8960(5)	126(5)
H(51B)	12610(4)	2518(15)	9117(9)	126(5)

Table 7. Torsion Angles [°] for α-Methylene Lactone 180

Atoms (1-2-3-4)	Angle	Atoms (1-2-3-4)	Angle
C(6)-O(1)-C(2)-C(3)	-44.0(3)	C(4)-C(3)-C(31)-O(3)	-103.7(3)
O(1)-C(2)-C(3)-O(3)	-73.0(3)	C(2)-C(3)-C(31)-O(3)	100.7(3)
O(1)-C(2)-C(3)-C(4)	61.7(3)	O(3)-C(3)-C(4)-C(42)	-37.7(4)
O(3)-C(3)-C(4)-C(5)	89.0(3)	C(2)-C(3)-C(4)-C(42)	-171.0(3)
C(2)-C(3)-C(4)-C(5)	-44.2(3)	C(42)-C(4)-C(5)-C(6)	137.3(4)
C(3)-C(4)-C(5)-C(6)	9.4(4)	C(51)-C(5)-C(6)-O(6)	15.9(6)
C(4)-C(5)-C(6)-O(1)	8.6(5)	C(51)-C(5)-C(6)-O(1)	-167.1(4)
C(2)-O(1)-C(6)-C(5)	10.4(4)	C(3)-C(4)-C(5)-C(51)	-175.1(4)
C(4)-C(5)-C(6)-O(6)	-168.3(4)	O(1)-C(2)-C(22)-O(22)	173.7(2)
C(2)-O(1)-C(6)-O(6)	-172.5(3)	C(3)-C(2)-C(22)-O(22)	-69.4(3)
C(31)-C(3)-C(4)-C(5)	158.6(3)	C(21)-C(2)-C(3)-C(31)	-23.6(4)
C(6)-O(1)-C(2)-C(21)	-167.7(3)	C(22)-C(2)-C(3)-C(31)	102.8(3)
C(6)-O(1)-C(2)-C(22)	74.3(3)	C(31)-C(3)-C(4)-C(42)	31.8(5)
C(21)-C(2)-C(3)-O(3)	44.1(4)	C(42)-C(4)-C(5)-C(51)	-47.2(6)
C(22)-C(2)-C(3)-O(3)	170.5(2)	O(1)-C(2)-C(22)-O(21)	-6.4(4)
O(1)-C(2)-C(3)-C(31)	-140.7(3)	C(3)-C(2)-C(22)-O(21)	110.5(3)
C(21)-C(2)-C(3)-C(4)	178.8(3)	C(21)-C(2)-C(22)-O(22)	59.6(3)
C(22)-C(2)-C(3)-C(4)	-54.9(3)	C(2)-C(22)-O(22)-C(23)	177.2(3)
C(4)-C(3)-O(3)-C(31)	113.7(3)	C(21)-C(2)-C(22)-O(21)	-120.5(4)
C(2)-C(3)-O(3)-C(31)	-113.0(4)	O(21)-C(22)-O(22)-C(23)	-2.7(5)

APPENDIX C
SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON SPIRODILACTONE 184

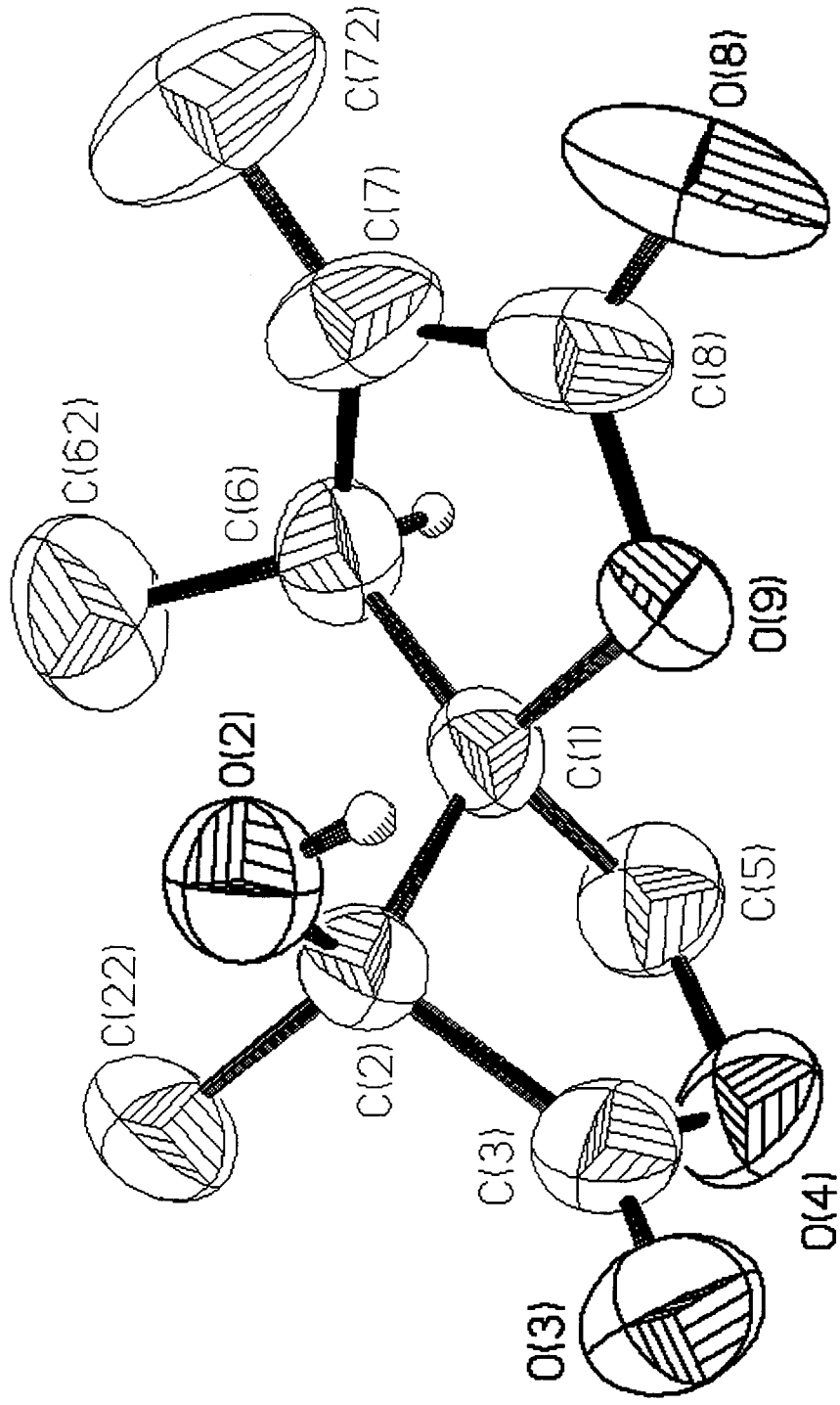

Table 1. Crystal Data and Structure Refinement for Spirodilactone 184

Identification code	STR4	
Empirical formula	$C_{10}H_{12}O_5$	
Formula weight	212.20	
Temperature	298(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.928(1) Å	$\alpha = 90°$
	b = 6.503(1) Å	$\beta = 91.222(6)°$
	c = 11.336(1) Å	$\gamma = 90°$
Volume	510.67(6) $Å^3$	
Z	2	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	0.950 mm^{-1}	
F(000)	224	
Crystal size	0.60 x 0.10 x 0.05 mm^3	
Theta range for data collection	6.39 to 57.43 °	
Index ranges	-7<=h<=5, -7<=k<=5, -12<=1<=12	
Reflections collected	1340	
Independent reflections	1100 [R(int) = 0.0235]	
Absorption correction	Empirical (Psi scans)	
Max. and min. transmission	0.9540 and 0.5994	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1100 / 1 / 149	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0879	
R indices (all data)	R1 = 0.0354, wR2 = 0.0896	
Absolute structure parameter	0.0(4)	
Extinction coefficient	0.023(2)	
Largest diff. peak and hole	0.109 and -0.102 $e.Å^{-3}$	

Table 2. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Spirodilactone 184

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(9)	4794(2)	9209(3)	8582(2)	54(1)
O(2)	2865(3)	5803(3)	7797(2)	63(1)
O(8)	4737(5)	9078(4)	10527(2)	101(1)
O(4)	5858(3)	9152(4)	6190(2)	76(1)
C(1)	3434(3)	9535(5)	7578(2)	47(1)
C(2)	3261(4)	7392(5)	7011(2)	48(1)
O(3)	6210(3)	5749(5)	6306(2)	84(1)
C(3)	5259(4)	7245(7)	6482(2)	62(1)
C(5)	4563(5)	10683(7)	6676(3)	70(1)
C(8)	3914(5)	9445(5)	9613(3)	64(1)
C(6)	1734(4)	10690(6)	8111(3)	61(1)
C(7)	1928(5)	10160(4)	9386(3)	70(1)
C(22)	1807(5)	7185(6)	5977(3)	74(1)
C(62)	-278(5)	10398(9)	7575(5)	117(2)
C(72)	635(8)	10189(6)	10240(5)	119(2)

Table 3. Bond Lengths [Å] for Spirodilactone 184

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O(9)	C(8)	1.339(3)	C(1)	C(2)	1.538(4)
O(9)	C(1)	1.477(3)	C(2)	C(3)	1.523(4)
O(2)	C(2)	1.395(3)	O(3)	C(3)	1.194(4)
O(8)	C(8)	1.196(4)	C(8)	C(7)	1.470(5)
O(4)	C(3)	1.351(4)	C(6)	C(7)	1.489(5)
O(4)	C(5)	1.456(4)	C(2)	C(22)	1.535(4)
C(1)	C(5)	1.500(4)	C(6)	C(62)	1.521(4)
C(1)	C(6)	1.532(4)	C(7)	C(72)	1.333(6)

Table 4. Bond Angles [°] for Spirodilactone 184

Atoms (1-2-3)	Angle	Atoms (1-2-3)	Angle
C(3)-C(2)-C(1)	99.1(2)	O(4)-C(5)-C(1)	104.6(3)
C(8)-O(9)-C(1)	111.2(2)	O(8)-C(8)-O(9)	121.1(3)
C(3)-O(4)-C(5)	109.9(2)	O(8)-C(8)-C(7)	129.9(3)
O(9)-C(1)-C(5)	105.3(2)	O(9)-C(8)-C(7)	109.0(3)
O(9)-C(1)-C(6)	104.4(2)	C(7)-C(6)-C(1)	102.4(2)
C(5)-C(1)-C(6)	116.2(3)	C(8)-C(7)-C(6)	108.0(3)
O(9)-C(1)-C(2)	103.5(2)	O(2)-C(2)-C(22)	106.7(2)
C(5)-C(1)-C(2)	101.7(2)	C(3)-C(2)-C(22)	106.3(2)
C(6)-C(1)-C(2)	123.7(2)	C(22)-C(2)-C(1)	116.2(2)
O(2)-C(2)-C(3)	113.5(3)	C(7)-C(6)-C(62)	115.0(4)
O(2)-C(2)-C(1)	114.8(2)	C(62)-C(6)-C(1)	119.1(3)
O(3)-C(3)-O(4)	122.3(3)	C(72)-C(7)-C(8)	121.2(4)
O(3)-C(3)-C(2)	128.7(3)	C(72)-C(7)-C(6)	130.8(4)
O(4)-C(3)-C(2)	109.0(3)		

Table 5. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Spirodilactone 184

The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [h^2a^{*2}U11 + ... + 2 h k a^* b^* U12]$

Atom	U11	U22	U33	U23	U13	U12
O(9)	52(1)	65(1)	44(1)	-5(1)	-6(1)	-4(1)
O(2)	67(1)	57(1)	64(1)	1(1)	5(1)	-10(1)
O(8)	183(3)	74(2)	44(1)	-8(1)	-24(2)	9(2)
O(4)	66(1)	104(2)	58(1)	11(1)	20(1)	-15(2)
C(1)	44(1)	54(2)	42(1)	4(1)	-4(1)	-7(1)
C(2)	49(1)	55(2)	40(1)	-2(1)	0(1)	-6(2)
O(3)	69(1)	109(2)	74(2)	-20(2)	10(1)	15(2)
C(3)	56(2)	90(3)	41(1)	-6(2)	2(1)	1(2)
C(5)	71(2)	75(2)	64(2)	16(2)	6(2)	-7(2)
C(8)	99(2)	47(2)	47(2)	-10(2)	6(2)	-2(2)
C(6)	51(2)	54(2)	77(2)	-9(2)	0(1)	2(2)
C(7)	96(2)	42(2)	73(2)	-9(2)	37(2)	-3(2)
C(22)	69(2)	87(3)	64(2)	-20(2)	-14(2)	-4(2)
C(62)	55(2)	126(4)	170(5)	-59(3)	-16(2)	20(2)
C(72)	160(4)	63(3)	137(4)	-1(2)	90(4)	9(3)

Table 6. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for Spirodilactone 184

Atom	x	y	z	U(eq)
H(2)	3829(4)	5630(5)	8280(3)	47(8)
H(5A)	3710(3)	11246(19)	6060(18)	84
H(5B)	5290(2)	11810(4)	7042(11)	84
H(6)	2030(13)	12160(6)	8046(4)	73
H(22A)	540(3)	7060(5)	6274(7)	110
H(22B)	2110(3)	6000(4)	5527(19)	110
H(22C)	1870(3)	8370(3)	5488(17)	110
H(62A)	-1220(3)	11320(6)	8000(3)	176
H(62B)	-690(3)	8910(5)	7670(3)	176
H(62C)	-268(14)	10770(6)	6700(3)	176
H(72A)	1010(4)	9719(18)	11060(3)	142
H(72B)	-710(5)	10683(18)	10068(8)	142

Table 7. Torsion Angles [°] for Spirodilactone 184

Atoms (1-2-3-4)	Angle	Atoms (1-2-3-4)	Angle
C(8)-O(9)-C(1)-C(5)	140.8(3)	C(1)-O(9)-C(8)-C(7)	-5.8(3)
C(8)-O(9)-C(1)-C(6)	17.9(3)	O(9)-C(1)-C(6)-C(7)	-21.9(3)
C(8)-O(9)-C(1)-C(2)	-112.8(2)	C(5)-C(1)-C(6)-C(7)	-137.3(3)
O(9)-C(1)-C(2)-O(2)	50.2(3)	C(2)-C(1)-C(6)-C(7)	95.7(3)
C(5)-C(1)-C(2)-O(2)	159.3(2)	O(8)-C(8)-C(7)-C(6)	171.2(4)
C(6)-C(1)-C(2)-O(2)	-67.8(3)	O(9)-C(8)-C(7)-C(6)	-9.3(4)
O(9)-C(1)-C(2)-C(3)	-71.0(2)	C(1)-C(6)-C(7)-C(8)	19.3(3)
C(5)-C(1)-C(2)-C(3)	38.1(2)	O(9)-C(1)-C(2)-C(22)	175.7(2)
C(6)-C(1)-C(2)-C(3)	171.0(3)	C(5)-C(1)-C(2)-C(22)	-75.3(3)
C(5)-O(4)-C(3)-O(3)	-170.9(3)	C(6)-C(1)-C(2)-C(22)	57.7(3)
C(5)-O(4)-C(3)-C(2)	10.3(3)	C(22)-C(2)-C(3)-O(3)	-88.5(4)
O(2)-C(2)-C(3)-O(3)	28.4(4)	C(22)-C(2)-C(3)-O(4)	90.1(3)
C(1)-C(2)-C(3)-O(3)	150.6(3)	O(9)-C(1)-C(6)-C(62)	-150.0(4)
O(2)-C(2)-C(3)-O(4)	-152.9(2)	C(5)-C(1)-C(6)-C(62)	94.5(5)
C(1)-C(2)-C(3)-O(4)	-30.7(3)	C(2)-C(1)-C(6)-C(62)	-32.5(5)
C(3)-O(4)-C(5)-C(1)	15.5(3)	O(8)-C(8)-C(7)-C(72)	-10.9(6)
O(9)-C(1)-C(5)-O(4)	73.7(3)	O(9)-C(8)-C(7)-C(72)	168.6(3)
C(6)-C(1)-C(5)-O(4)	-171.3(2)	C(1)-C(6)-C(7)-C(72)	-158.4(4)
C(2)-C(1)-C(5)-O(4)	-34.0(3)	C(62)-C(6)-C(7)-C(8)	150.0(3)
C(1)-O(9)-C(8)-O(8)	173.8(3)	C(62)-C(6)-C(7)-C(72)	-27.6(6)

APPENDIX D
SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON (-)-SWAZINE (2)

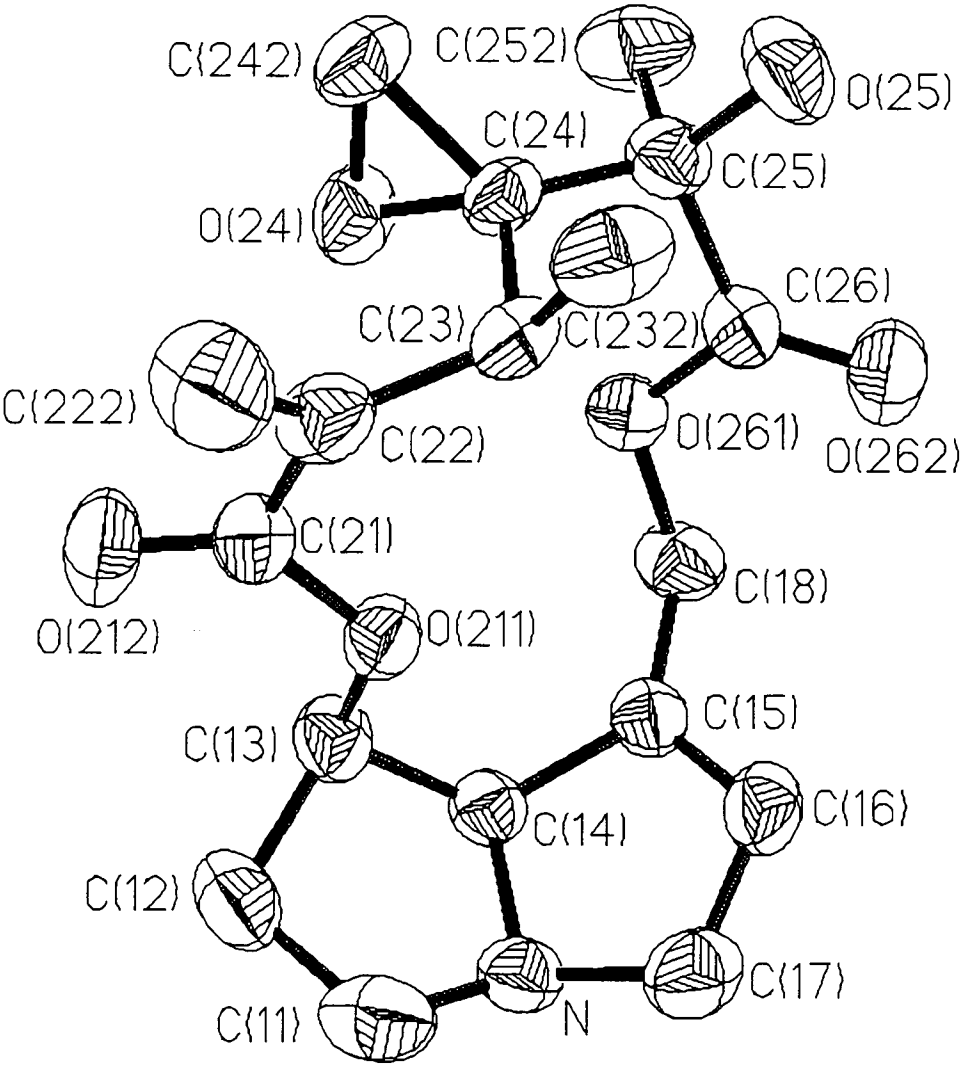

Table 1. Crystal Data and Structure Refinement for Swazine (2)

Empirical formula	$C_{18}H_{23}NO_6$	
Formula Weight	349.37	
Temperature	293 (2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.9400(10) Å	$\alpha = 90°$
	b = 12.2290(10) Å	$\beta = 90°$
	c = 16.7060(10) Å	$\gamma = 90°$
Volume	1826.4(3) $Å^3$	
Z	4	
Density (calculated)	1.271 Mg/m^3	
Absorption coefficient	0.795 mm^{-1}	
F(000)	744	
Theta range for data collection	4.48 to 56.73 °	
Index ranges	-1<=h<=9, -1<=k<=13, -1<=1<=18	
Reflections collected	1936	
Independent reflections	1775 [R(int) = 0.0335]	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1775 / 0 / 251	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0971	
R indices (all data)	R1 = 0.0365, wR2 = 0.0979	
Absolute structure parameter	0.4(3)	
Extinction coefficient	0.0226(12)	
Largest diff. peak and hole	0.131 and -0.151 $e.Å^{-3}$	

Table 2. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Swazine (2)

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N	8894(2)	4086(2)	5320(1)	47(1)
C(11)	10450(4)	4319(3)	5523(2)	67(1)
C(12)	10469(4)	5533(3)	5696(2)	62(1)
C(13)	9390(3)	5986(2)	5084(2)	46(1)
C(14)	8161(3)	5141(2)	5096(1)	42(1)
C(15)	7307(3)	4865(2)	4345(1)	42(1)
C(16)	7573(4)	3844(2)	4135(2)	53(1)
C(17)	8647(4)	3291(2)	4675(2)	60(1)
C(18)	6230(3)	5623(2)	3953(2)	51(1)
C(21)	11053(3)	6767(2)	4127(2)	49(1)
O(211)	10047(2)	5978(1)	4289(1)	43(1)
O(212)	11485(3)	7410(2)	4623(1)	75(1)
C(22)	11573(3)	6696(2)	3281(2)	49(1)
C(222)	12986(4)	6929(3)	3145(2)	80(1)
C(23)	10439(3)	6373(2)	2655(2)	41(1)
C(232)	11157(4)	6002(2)	1877(2)	58(1)
C(24)	9339(3)	7320(2)	2526(1)	38(1)
O(24)	9254(2)	8092(1)	3171(1)	52(1)
C(242)	9942(4)	8424(2)	2431(2)	53(1)
C(25)	7817(3)	7032(2)	2156(1)	44(1)
O(25)	8142(2)	6672(2)	1379(1)	62(1)
C(252)	6724(4)	7993(3)	2143(2)	67(1)
C(26)	7088(3)	6118(2)	2647(1)	44(1)
O(261)	6969(2)	6394(1)	3416(1)	45(1)
O(262)	6646(3)	5274(2)	2368(1)	74(1)

Table 3. Bond Lengths [Å] for Swazine (2)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
N	C(11)	1.459(4)	C(242)	H(1)	0.97(4)
N	C(17)	1.469(3)	C(242)	H(2)	1.00(4)
N	C(14)	1.495(3)	O(25)	H(25)	0.91(4)
C(11)	C(12)	1.513(5)	C(25)	C(26)	1.531(4)
C(12)	C(13)	1.512(4)	C(18)	O(261)	1.460(3)
C(21)	C(22)	1.490(4)	C(21)	O(212)	1.206(3)
C(22)	C(23)	1.509(4)	C(21)	O(211)	1.346(3)
C(23)	C(24)	1.534(3)	C(13)	O(211)	1.452(3)
C(24)	O(24)	1.435(3)	C(22)	C(222)	1.315(4)
C(13)	C(14)	1.508(4)	C(23)	C(232)	1.520(4)
C(14)	C(15)	1.507(3)	C(24)	C(242)	1.462(4)
C(15)	C(16)	1.319(4)	O(24)	C(242)	1.438(4)
C(15)	C(18)	1.489(4)	C(25)	C(252)	1.529(4)
C(16)	C(17)	1.481(4)	C(26)	O(262)	1.200(3)
C(24)	C(25)	1.535(4)	C(26)	O(261)	1.333(3)
C(25)	O(25)	1.401(3)			

Table 4. Bond Angles [°] for Swazine (2)

Atoms (1-2-3)	Angle	Atoms (1-2-3)	Angle
C(11)-N-C(17)	116.2(3)	H(1)-C(242)-H(2)	119(3)
C(11)-N-C(14)	107.9(2)	H(1)-C(242)-C(24)	118(2)
N-C(17)-C(16)	104.0(2)	C(22)-C(23)-C(232)	112.8(2)
N-C(11)-C(12)	104.3(3)	C(232)-C(23)-C(24)	112.1(2)
N-C(14)-C(13)	106.0(2)	O(261)-C(18)-C(15)	112.3(2)
C(17)-N-C(14)	108.78(19)	C(24)-O(24)-C(242)	61.18(16)
N-C(14)-C(15)	103.71(19)	O(212)-C(21)-C(22)	126.1(2)
C(14)-C(13)-C(12)	101.8(2)	O(211)-C(21)-C(22)	111.0(2)
C(13)-C(12)-C(11)	102.9(2)	C(222)-C(22)-C(21)	116.9(3)
C(13)-C(14)-C(15)	120.8(2)	C(222)-C(22)-C(23)	125.5(3)
C(16)-C(15)-C(18)	126.1(3)	C(242)-C(24)-C(23)	118.4(2)
C(16)-C(15)-C(14)	110.1(2)	O(211)-C(13)-C(12)	111.0(2)
C(18)-C(15)-C(14)	123.6(2)	C(242)-C(24)-C(25)	119.7(2)
C(15)-C(16)-C(17)	112.7(3)	O(25)-C(25)-C(252)	111.1(2)
C(21)-C(22)-C(23)	117.6(2)	O(262)-C(26)-C(25)	124.0(2)
C(22)-C(23)-C(24)	109.3(2)	O(261)-C(26)-C(25)	111.4(2)
O(24)-C(24)-C(23)	115.2(2)	C(26)-O(261)-C(18)	117.7(2)
O(24)-C(24)-C(25)	114.0(2)	C(252)-C(25)-C(26)	107.2(2)
H(1)-C(242)-O(24)	116(2)	C(252)-C(25)-C(24)	113.3(2)
O(25)-C(25)-C(26)	110.8(2)	O(24)-C(242)-C(24)	59.30(16)
O(25)-C(25)-C(24)	105.2(2)	O(24)-C(24)-C(242)	59.52(17)
C(26)-C(25)-C(24)	109.2(2)	C(21)-O(211)-C(13)	116.70(19)
H(25)-O(25)-C(25)	116(2)	O(211)-C(13)-C(14)	107.60(19)
H(2)-C(242)-C(24)	114(2)	O(212)-C(21)-O(211)	122.9(2)
H(2)-C(242)-O(24)	116(2)	O(262)-C(26)-O(261)	124.5(2)
C(23)-C(24)-C(25)	116.84(19)		

Table 5. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Swazine (2)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2a^{*2}U11 + ... + 2 h k a^* b^* U12]$

Atom	U11	U22	U33	U23	U13	U12
N	57(1)	46(1)	39(1)	4(1)	-1(1)	4(1)
C(11)	60(2)	71(2)	71(2)	22(2)	-3(2)	9(2)
C(12)	59(2)	84(2)	44(1)	3(2)	-9(1)	-15(2)
C(13)	51(1)	49(1)	39(1)	-6(1)	1(1)	-2(1)
C(14)	47(1)	43(1)	35(1)	0(1)	2(1)	1(1)
C(15)	44(1)	48(1)	34(1)	3(1)	3(1)	-9(1)
C(16)	67(2)	51(2)	40(1)	-7(1)	4(1)	-13(1)
C(17)	84(2)	47(1)	48(1)	-2(1)	7(2)	6(2)
C(18)	43(1)	64(2)	45(1)	13(1)	2(1)	-6(1)
C(21)	45(1)	47(1)	54(2)	4(1)	-9(1)	-7(1)
O(211)	46(1)	41(1)	41(1)	-1(1)	2(1)	-8(1)
O(212)	89(2)	70(1)	67(1)	-7(1)	-15(1)	-37(1)
C(22)	41(1)	46(1)	60(2)	10(1)	2(1)	-3(1)
C(222)	47(2)	113(3)	79(2)	17(2)	0(2)	-17(2)
C(23)	45(1)	30(1)	47(1)	3(1)	8(1)	0(1)
C(232)	70(2)	45(1)	58(2)	2(1)	21(2)	12(1)
C(24)	50(1)	27(1)	39(1)	-2(1)	6(1)	0(1)
O(24)	64(1)	40(1)	53(1)	-16(1)	6(1)	0(1)
C(242)	68(2)	31(1)	60(2)	1(1)	8(2)	-2(1)
C(25)	50(1)	45(1)	37(1)	1(1)	1(1)	1(1)
O(25)	65(1)	86(1)	35(1)	-7(1)	0(1)	-14(1)
C(252)	58(2)	65(2)	79(2)	24(2)	-1(2)	16(2)
C(26)	46(1)	46(1)	41(1)	-1(1)	-6(1)	-1(1)
O(261)	52(1)	47(1)	38(1)	4(1)	1(1)	-5(1)
O(262)	104(2)	63(1)	54(1)	-7(1)	-3(1)	-34(1)

Table 6. Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for Swazine (2)

Atom	x	y	z	U(eq)
H(11A)	11073(17)	4152(5)	5102(11)	72(2)
H(11B)	10744(9)	3924(11)	5966(11)	73(2)
H(12A)	10146(9)	5677(5)	6213(14)	73(2)
H(12B)	11420(3)	5822(8)	5628(2)	73(2)
H(13)	9009(13)	6740(3)	5239(5)	73(2)
H(14)	7380(3)	5354(8)	5552(16)	73(2)
H(16)	7122(18)	3498(13)	3683(17)	73(2)
H(17A)	8220(11)	2602(18)	4888(6)	73(2)
H(17B)	9590(2)	3124(5)	4393(7)	73(2)
H(18A)	5518(19)	5208(11)	3657(8)	73(2)
H(18B)	5703(14)	6020(10)	4355(10)	73(2)
H(22A)	13666(18)	7144(7)	3605(11)	73(2)
H(22B)	13396(11)	6894(3)	2578(14)	73(2)
H(23)	9880(2)	5770(2)	2863(8)	73(2)
H(23A)	11630(2)	6625(12)	1615(8)	73(2)
H(23B)	10391(15)	5697(16)	1525(8)	73(2)
H(23C)	11910(2)	5444(16)	1990(3)	73(2)
H(1)	9370(4)	8950(3)	2114(19)	73(2)
H(2)	11060(5)	8470(3)	2440(2)	73(2)
H(25)	7360(5)	6390(3)	1100(2)	73(2)
H(25A)	6586(17)	8286(12)	2711(11)	73(2)
H(25B)	5720(2)	7737(6)	1924(11)	73(2)
H(25C)	7139(13)	8598(13)	1785(11)	73(2)

Table 7. Torsion Angles [°] for Swazine (2)

Atoms (1-2-3-4)	Angle
C(17)-N-C(11)-C(12)	141.8(2)
C(14)-N-C(11)-C(12)	19.4(3)
N-C(11)-C(12)-C(13)	-37.6(3)
C(11)-N-C(17)-C(16)	-130.3(3)
C(14)-N-C(17)-C(16)	-8.3(3)
C(15)-C(16)-C(17)-N	6.3(3)
C(11)-N-C(14)-C(13)	6.2(3)
C(17)-N-C(14)-C(13)	-120.7(2)
C(11)-N-C(14)-C(15)	134.4(2)
C(17)-N-C(14)-C(15)	7.4(3)
N-C(14)-C(15)-C(18)	171.7(2)
N-C(14)-C(15)-C(16)	-3.6(3)
C(12)-C(13)-C(14)-N	-29.1(2)
O(211)-C(13)-C(14)-N	87.7(2)
C(21)-C(22)-C(23)-C(24)	71.7(3)
C(22)-C(23)-C(24)-O(24)	-21.0(3)
C(12)-C(13)-C(14)-C(15)	-146.3(2)
C(13)-C(14)-C(15)-C(16)	114.8(3)
C(13)-C(14)-C(15)-C(18)	-70.0(3)
C(18)-C(15)-C(16)-C(17)	-176.8(2)
C(14)-C(15)-C(16)-C(17)	-1.6(3)
C(22)-C(23)-C(24)-C(25)	-158.8(2)
C(24)-O(24)-C(242)-H(1)	109(2)
C(24)-O(24)-C(242)-H(2)	-104(2)
O(24)-C(24)-C(242)-H(1)	-104(2)
C(23)-C(24)-C(242)-H(1)	151(2)
C(25)-C(24)-C(242)-H(1)	-2(2)
O(24)-C(24)-C(242)-H(2)	107(2)
C(23)-C(24)-C(242)-H(2)	3(2)
C(25)-C(24)-C(242)-H(2)	-151(2)

Table 7. Torsion Angles [°] for Swazine (2) (continued)

Atoms (1-2-3-4)	Angle
C(23)-C(24)-C(25)-O(25)	-65.5(3)
O(24)-C(24)-C(25)-C(26)	-84.8(2)
C(23)-C(24)-C(25)-C(26)	53.5(3)
C(11)-C(12)-C(13)-C(14)	40.7(3)
C(26)-C(25)-O(25)-H(25)	55(2)
C(24)-C(25)-O(25)-H(25)	173(2)
O(24)-C(24)-C(25)-O(25)	156.20(19)
C(22)-C(21)-O(211)-C(13)	-177.0(2)
C(14)-C(13)-O(211)-C(21)	172.5(2)
C(12)-C(13)-O(211)-C(21)	-76.9(3)
O(211)-C(13)-C(14)-C(15)	-29.5(3)
C(16)-C(15)-C(18)-O(261)	-101.0(3)
C(14)-C(15)-C(18)-O(261)	84.5(3)
O(212)-C(21)-C(22)-C(23)	-145.3(3)
O(211)-C(21)-C(22)-C(23)	36.8(3)
C(21)-C(22)-C(23)-C(232)	-162.9(2)
C(222)-C(22)-C(23)-C(24)	-107.9(3)
C(232)-C(23)-C(24)-O(24)	-146.8(2)
C(22)-C(23)-C(24)-C(242)	46.5(3)
C(232)-C(23)-C(24)-C(25)	75.4(3)
C(23)-C(24)-O(24)-C(242)	109.5(3)
C(25)-C(24)-O(24)-C(242)	-111.5(3)
C(23)-C(24)-C(242)-O(24)	-104.0(2)
C(25)-C(24)-C(242)-O(24)	102.0(2)
C(242)-C(24)-C(25)-O(25)	88.9(3)
O(24)-C(24)-C(25)-C(252)	34.7(3)
C(23)-C(24)-C(25)-C(252)	173.0(2)
C(242)-C(24)-C(25)-C(26)	-152.1(2)
O(25)-C(25)-C(26)-O(262)	-10.7(4)
C(24)-C(25)-C(26)-O(262)	-126.1(3)

Table 7. Torsion Angles [°] for Swazine (2) (continued)

Atom (1-2-3-4)	Angle
O(25)-C(25)-C(26)-O(261)	171.0(2)
C(24)-C(25)-C(26)-O(261)	55.6(3)
C(25)-C(26)-O(261)-C(18)	177.2(2)
C(15)-C(18)-O(261)-C(26)	92.7(3)
C(252)-C(25)-O(25)-H(25)	-64(2)
C(11)-C(12)-C(13)-O(211)	-73.6(3)
C(242)-C(24)-C(25)-C(252)	-32.6(3)
C(232)-C(23)-C(24)-C(242)	-79.3(3)
O(212)-C(21)-C(22)-C(222)	34.3(5)
O(211)-C(21)-C(22)-C(222)	-143.6(3)
O(212)-C(21)-O(211)-C(13)	5.1(4)
C(222)-C(22)-C(23)-C(232)	17.5(4)
O(262)-C(26)-O(261)-C(18)	-1.0(4)
C(252)-C(25)-C(26)-O(261)	-67.6(3)
C(252)-C(25)-C(26)-O(262)	110.7(3)